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PART I: THE SYNTHESIS OF MERCAPTOINDOLES

PART II: THE REARRANGEMENT OF ALLYL 2,6-DIHALOPHENYL
ETHERS

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF
DOCTOR OF PHILOSOPHY

BY

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PART I: THE SYNTHESIS OF MERCAPTOPYRIMIDINES

Treatment of 5-bromo-2-nitrotoluene with potassium benzyl
mercaptide in dimethyl sulfoxide solution gave 5-benzylthio-
2-nitrotoluene. Condensation of the latter with ethyl oxalate

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PART II: THE REARRANGEMENT OF ALLYL 2,6-DICHLOROPHENYL ETHERS

The zinc chloride-catalyzed rearrangement of allyl 2,6-di-
chlorophenyl ether in nitrobenzene solution gave a good yield
of 2-allyl-4,6-dichlorophenol, along with some 2,6-dichlorophenol
and 5,7-dichloro-2-methylcoumaran. The coumaran was formed by
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phenol and 2-allyl-4,6-dichlorophenol.

A study of the thermal rearrangement of allyl 2,6-dichloro-

ABSTRACTS

PART I: THE SYNTHESIS OF MERCAPTOINDOLES

Treatment of 6-bromo-2-nitrotoluene with potassium benzyl mercaptide in dimethylformamide solution gave 6-benzylthio-2-nitrotoluene. Condensation of the latter with ethyl oxalate in the presence of potassium ethoxide in ether solution afforded the potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate which, upon reductive cyclization by ferrous sulphate and ammonium hydroxide, yielded 4-benzylthioindole-2-carboxylic acid. Decarboxylation of this acid in hot quinoline, using as catalyst a small amount of its copper salt, produced 4-benzylthioindole. Reductive cleavage of the thioether linkage of the latter compound by treatment with sodium in liquid ammonia, afforded 4-mercaptoindole.

Similarly, 7-mercaptoindole was prepared from 3-bromo-2-nitrotoluene.

PART II: THE REARRANGEMENT OF ALLYL 2,6-DIHALOPHENYL ETHERS

The zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether in nitrobenzene solution gave a good yield of 2-allyl-4,6-dichlorophenol, along with some 2,6-dichlorophenol and 5,7-dichloro-2-methylcoumaran. The coumaran was formed by ring closure of the 2-allyl-4,6-dichlorophenol. These results are in contrast to those obtained from the thermal rearrangement of this ether in nitrobenzene, which gave mainly 4-allyl-2,6-dichlorophenol, along with smaller amounts of 2-allyl-6-chlorophenol and 2-allyl-4,6-dichlorophenol.

A study of the thermal rearrangement of allyl 2,6-dichloro-

phenyl ether in a number of solvents of different dielectric constant revealed that halogen migration, to form 2-allyl-4,6-dichlorophenol, proceeded somewhat better in highly polar solvents. However, a competitive reductive removal of halogen to form 2-allyl-6-chlorophenol occurred in the presence of oxidizable solvents and/or products. The reaction was also complicated by the catalytic effects of certain solvents and phenolic products.

Rearrangement of allyl 2,6-dichlorophenyl ether in the presence of stannous chloride showed that this metal halide catalyzed the reaction as well as promoted halogen rearrangement. A competitive reductive removal of the halogen also took place.

Results from the rearrangement of allyl 2,6-dibromophenyl ether in the presence of zinc chloride and of allyl 2,6-dichlorophenyl ether in the presence of zinc bromide, showed that halogen migration and halogen substitution took place during these reactions. Possible mechanisms for these transformations are presented.

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ETHERS

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PART I

THE SYNTHESIS

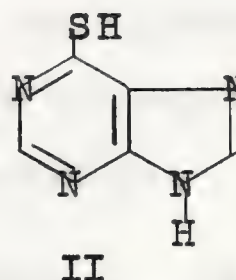
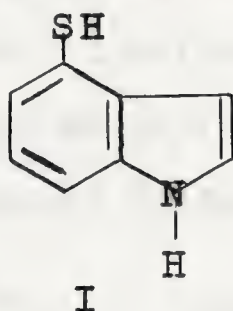
OF

MERCAPTOINDOLES

INTRODUCTION

1. The Problem.

Interest in the synthesis of 4-mercaptoindole (I) arose from the observation that the structurally analogous 6-mercaptapurine (II) has been successfully employed in the treatment of some forms of cancer (1, 2). Due to the



close structural resemblance of 4-mercaptoindole to the chemotherapeutic 6-mercaptapurine, it was felt that the former compound might also exhibit some anticarcinogenic properties.

Although a synthesis of the 2- and 3-mercaptoindoles was described by Oddo and Mingoa in 1932 (3), no report, prior to the commencement of our work, existed in the literature concerning the preparation of benzene-ring substituted mercaptoindoles. It was thought of interest, therefore, to prepare the 5-, 6- and 7-mercaptoindoles, as well as the 4- isomer, in order that they might become available for physiological testing.

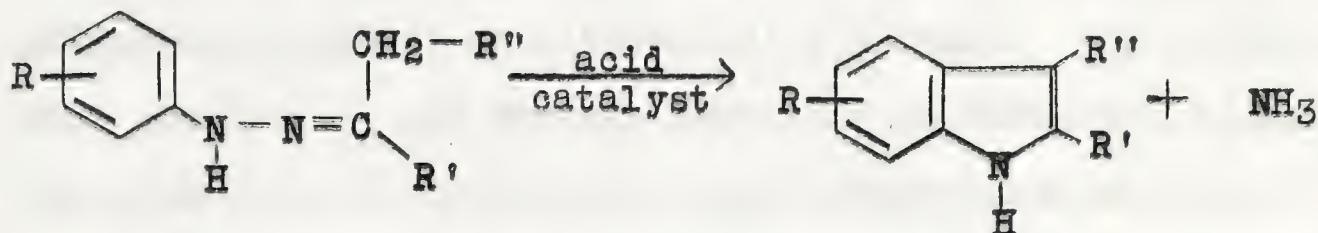
2. General Methods for the Preparation of Indoles and Mercaptans.

Two main structural features are required in the preparation of mercaptoindoles. One is that of formation of the indole ring system and the other of introduction of the mercapto (-SH) substituent at the appropriate position(s) in the benzene ring. A brief outline of methods which could be used to achieve these

two goals may be of assistance in understanding the present problem.

A. Methods of Preparation of Indoles.

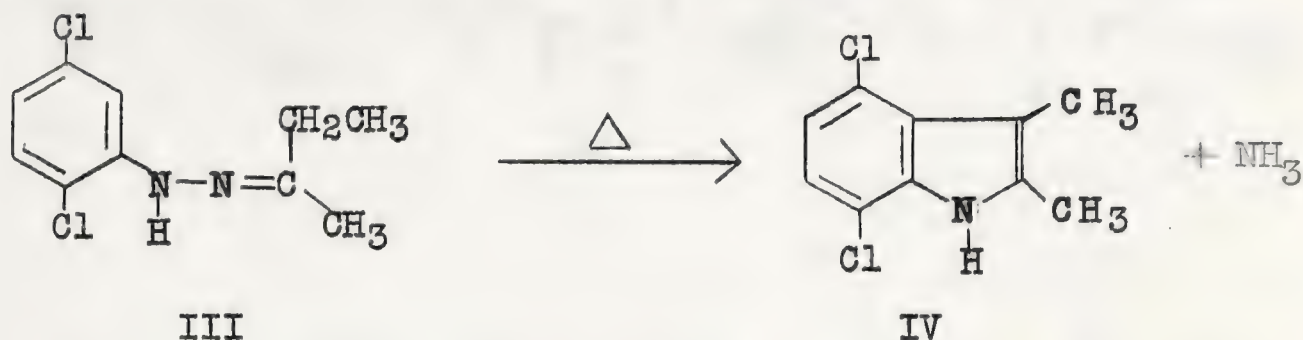
Of the number of general methods available for the preparation of indole and its derivatives, the synthesis discovered by Emil Fischer (4) has proven to be the most versatile. Fischer's synthesis involves the cyclization of phenylhydrazones of alkyl or aralkyl ketones, aldehydes, or keto-acids, and can be illustrated by the following general reaction:



The direct preparation of indole itself from acetaldehyde phenylhydrazone by this method has not yet been accomplished (5). However, indole can be obtained by decarboxylation of indole-2-carboxylic acid, which in turn is prepared by Fischer cyclization of the phenylhydrazone of pyruvic acid (6).

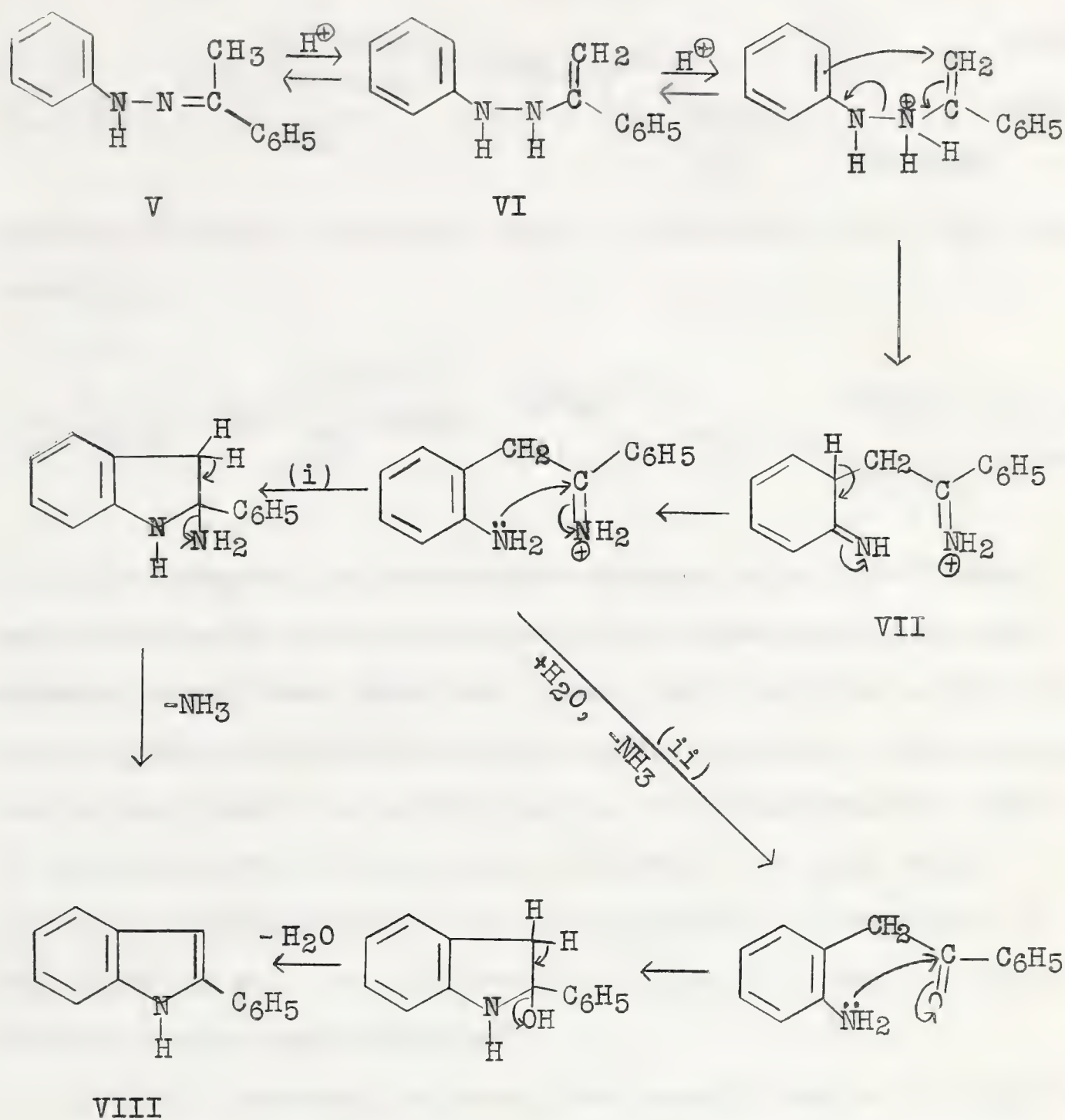
Although acidic catalysts, such as zinc chloride, stannic chloride, boron trifluoride, phosphoric acid, etc. are usually employed to effect the cyclization in the Fischer reaction, a number of phenylhydrazones have also been thermally cyclized to the corresponding indoles. Thus, Wolff (7) reported that distillation of acetophenone phenylhydrazone gave a small yield of 2-phenylindole. More recently, Fitzpatrick and Hiser (8) successfully cyclized several hydrazones by refluxing the latter in a high boiling solvent. For example, when the 2,5-dichloro-

phenylhydrazone of methyl ethyl ketone (III) was heated for six hours in refluxing ethylene glycol, a 66% yield of 4,7-dichloro-2,3-dimethylindole (IV) was isolated.



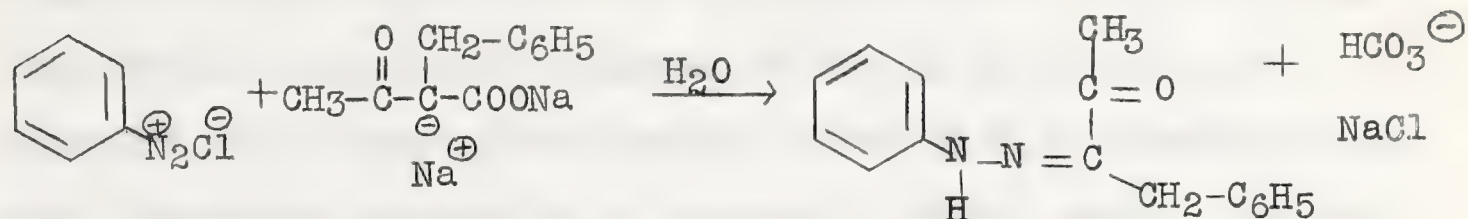
Indoles have also been obtained by thermal rearrangement of the corresponding phenylhydrazones in the presence of sodium hydroxide, with (8) or without (9) a solvent. The use of an acid catalyst in the Fischer synthesis is therefore apparently not essential if sufficiently high temperatures are used.

The nature of the mechanism of the Fischer indole synthesis has been the subject of much research effort. Although a number of mechanistic schemes have been advanced, the proposal by Robinson and Robinson in 1918 (10, 11), extended by Allen and Wilson in 1943 (12), has proved to be the most satisfactory one in explaining the various facets of the reaction. This mechanism may be conveniently illustrated by the cyclization of acetophenone phenylhydrazone (V) to 2-phenylindole (VIII), and consists essentially of three separate stages: (a) hydrazone - enehydrazine equilibration ($\text{V} \rightleftharpoons \text{VI}$); (b) formation of a new carbon-carbon bond ($\text{VI} \rightarrow \text{VII}$), via a dienone imine intermediate; (c) aromatization followed by cyclization and then loss of ammonia [by either route (i) or (ii)].

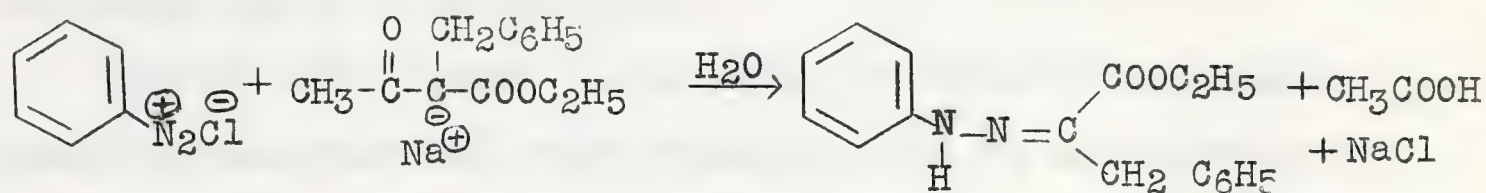


The scope of the Fischer indole synthesis is widened by the use of the Japp-Klingemann reaction (13) as an alternative method for the preparation of arylhydrazones. In this reaction, an aryldiazonium chloride is coupled with the sodium salt of a β -keto acid yielding an arylhydrazone through elimination of the carboxyl group, as exemplified in the reaction below. If

the carboxyl group in the keto acid structure is protected

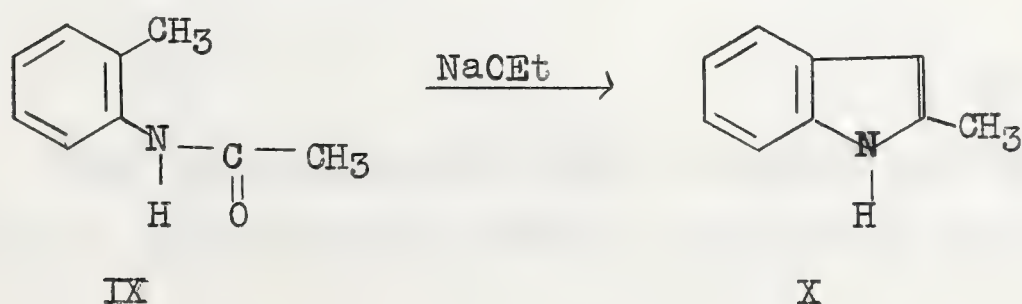


by esterification, the acyl group is eliminated rather than the carboxyl.



In attempting to produce mercaptoindoles by the Fischer indole synthesis from arylamines which already contained the mercapto substituent Brown and Kutney (14), in this laboratory, treated p-chloronitrobenzene with sodium sulphide, thus replacing the halogen atom by a mercapto group, with simultaneous reduction of the nitro group to the amine. However, the next step, involving diazotization of the amine followed by reduction of the diazonium salt, was unsuccessful since they were unable to isolate a pure phenylhydrazine.

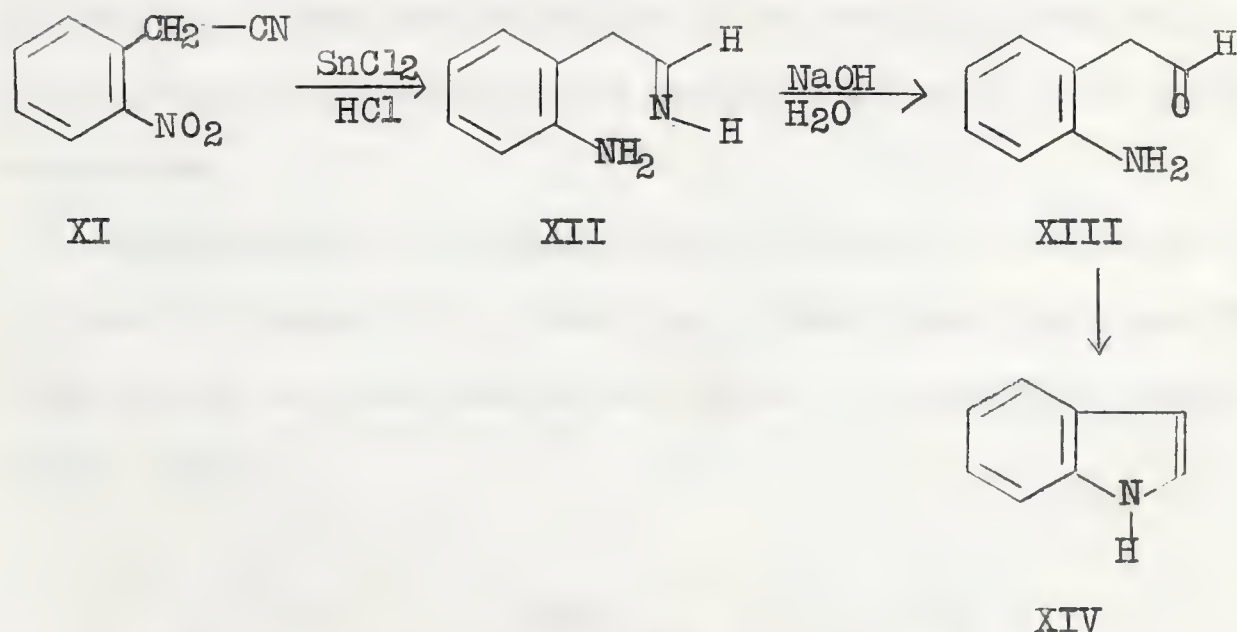
In 1912, Madelung reported that 2-methylindole (X) could be prepared by heating o-acetotoluidide (IX) with sodium ethoxide in the absence of air (15). Although, with the passage of years



this method of preparing indole derivatives has proven to be of limited general applicability, the Madelung reaction has been successfully applied to a number of N-acyl derivatives of o-toluidines. Tyson, for example, found that o-formotoluidide, with potassium t-butoxide as condensing agent, gave a 79% yield of indole (16).

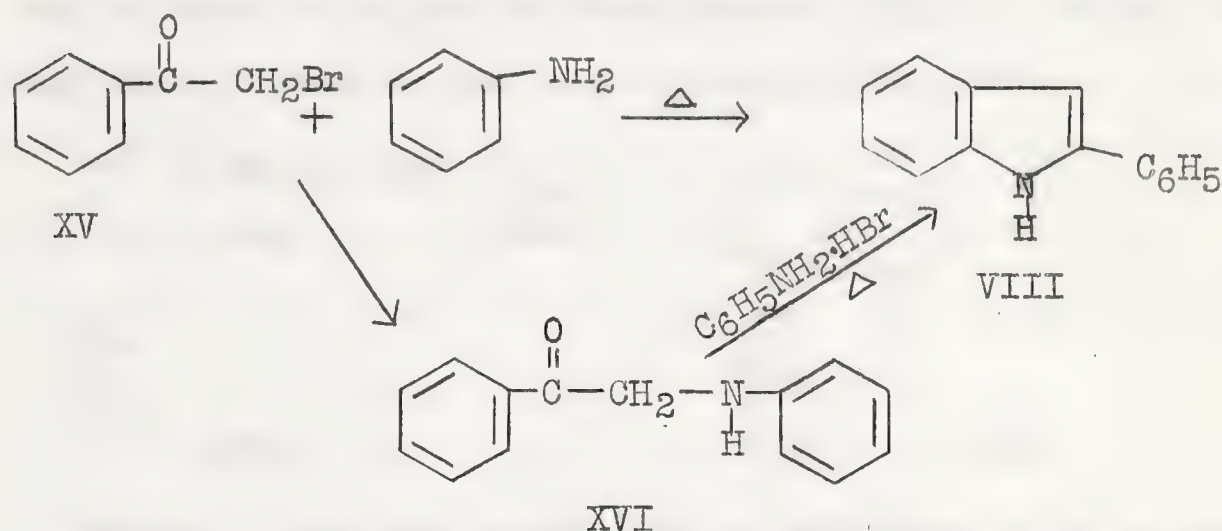
The mechanism of the Madelung reaction has received scant attention and is thus uncertain.

Stephen (17) formed indole (XIV) by reduction of o-nitrophenylacetonitrile (XI) with stannous chloride and hydrogen chloride in anhydrous ether, followed by decomposition of the reduction product (XII) by aqueous alkali. This reaction is actually an extension of Stephen's aldehyde synthesis, and one of the proposed intermediates in the present example was, in fact, o-aminophenylacetaldehyde (XIII).



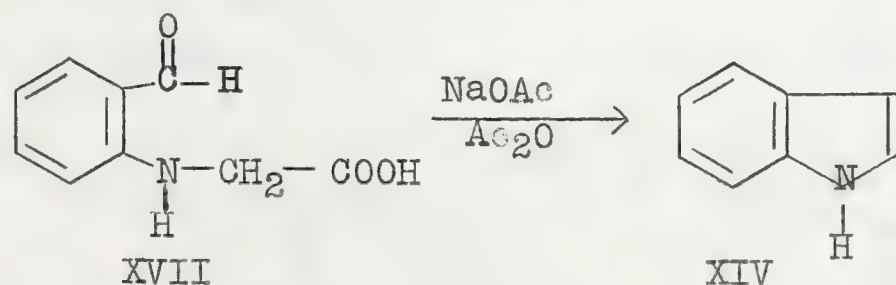
When phenacyl bromide (XV) is heated with an excess of aniline, 2-phenylindole (VIII) is formed in good yield. Further

more, by limiting the quantity of aniline there may be isolated N-phenacylaniline (XVI) which, when heated with aniline in the presence of aniline hydrohalide, yields 2-phenylindole (VIII). This reaction, first discovered by Möhlau (18) and

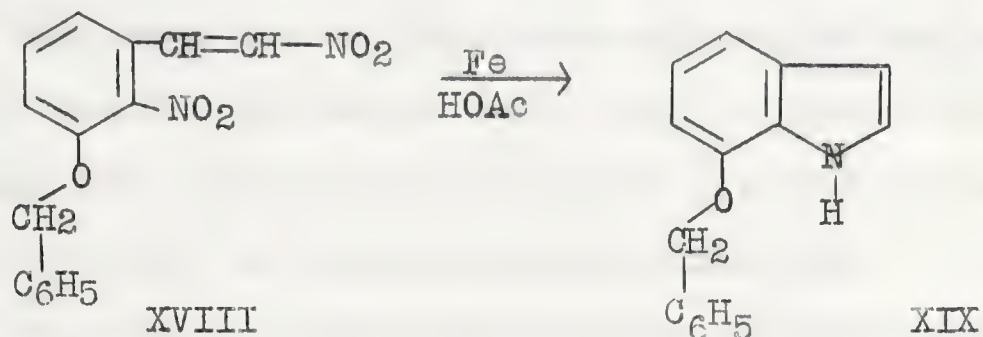


extended by Bischler (19, 20) is the parent of a general class of reactions for the synthesis of substituted indoles from α -halo, α -arylamino, and α -hydroxy ketones. Although no completely generalized formulation can be given to this synthetic approach, it has been utilized for the preparation of a variety of indolic substances.

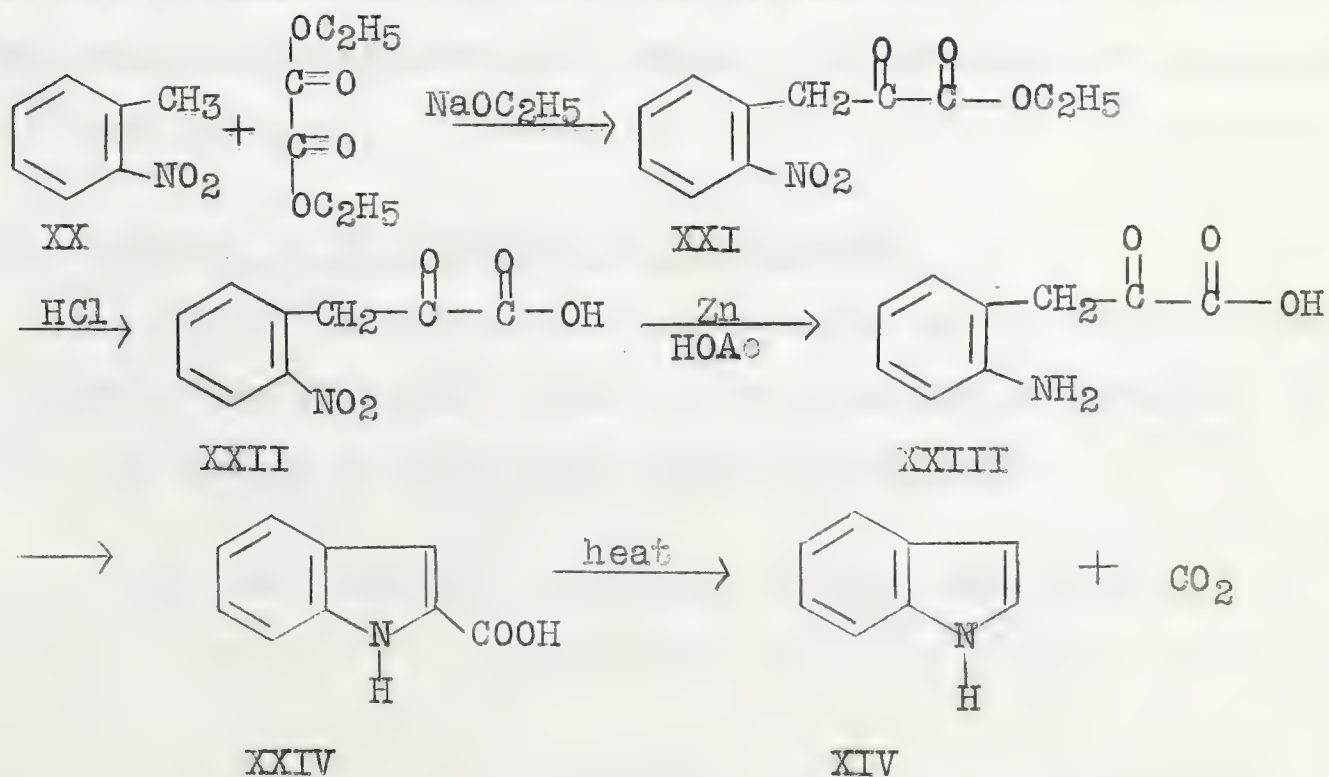
Reminiscent of the Madelung synthesis of indoles is that devised by Gluud (21). Heating *o*-formylphenylglycine (XVII) with sodium acetate-acetic anhydride is stated to yield 80% of indole (XIV).



There are several methods for the preparation of indoles in which the hetero ring is formed by cyclization of a two-carbon chain in an o-aminophenyl compound. For example, Ek and Witkop (22) were able to obtain 7-(or 5-)benzyloxyindoles (XIX) from 3-(or 5-)benzyloxy-o,o-dinitrostyrenes (XVIII), respectively, by the Nenitzescu-van der Lee synthesis (23, 24).



Probably the best known indole synthesis of this general type is the Reissert synthesis (25), which has been of value for the preparation of a variety of substituted indoles. This synthesis can be readily illustrated by Reissert's original preparation. Condensation of o-nitrotoluene (XX) with ethyl oxalate in the presence of sodium ethoxide affords ethyl o-nitrophenylpyruvate (XXI). After acid hydrolysis



of the ester, the resulting o-nitrophenylpyruvic acid (XXII), is reduced with zinc and acetic acid to the intermediate o-amino-phenylpyruvic acid (XXIII) which undergoes cyclization with loss of water under the conditions of the reduction. The isolated product is thus indole-2-carboxylic acid (XXIV), which, when heated above its melting point, is decarboxylated to indole (XIV).

The reduction of the intermediate o-nitrophenylpyruvic acid (XXII) can be carried out with zinc in acetic acid (25), zinc amalgam and hydrochloric acid (26), ferrous sulphate and ammonium hydroxide (27) or sodium hydrosulphite (28).

This method, as outlined above, is applicable, for the most part, to the preparation of indoles substituted in the aromatic ring. It involves, of course, the synthesis of the desired o-nitrotoluene with the substituent(s) in the proper position on the ring. For example, Blaikie and Perkin (29) prepared the 4-, 5- and 7-methoxyindoles from the corresponding 6-, 5- and 3-methoxy-2-nitrotoluenes, respectively.

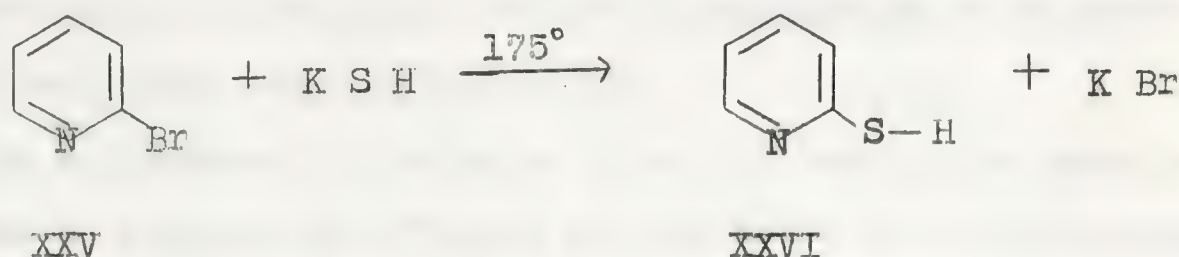
In a study of various methods for the preparation of indole, Shorygin and Polyakova (30) found that the Reissert method gave optimum results.

B. Methods of Preparation of Mercaptans.

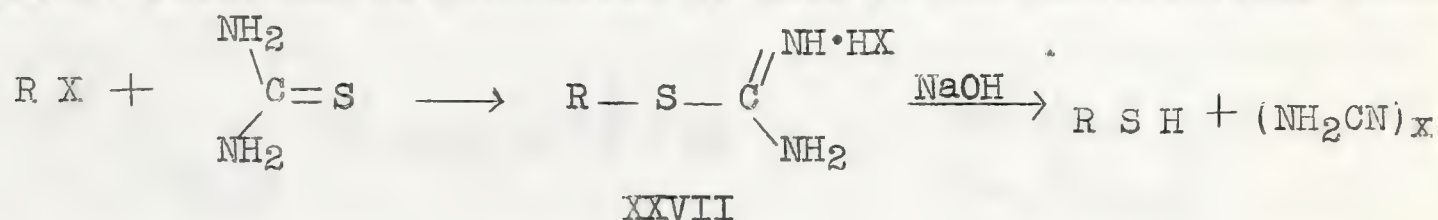
A direct introduction of a mercapto group into an organic molecule can be accomplished by the reaction of hydrogen sulphide (31) or sodium or potassium hydrosulphide with



alkylating agents such as alkyl sulphates, primary or secondary alkyl halides, or reactive aromatic halides. Thus, for example, potassium hydrosulphide in propylene glycol at 175° converts 2-bromopyridine (XXV) to 2-mercaptopyridine (XXVI) in 87% yield (32).



The reaction of thiourea with compounds containing sufficiently reactive halogens produces isothiocarbonium salts (XXVII) which can be hydrolyzed by base to the corresponding thiol.



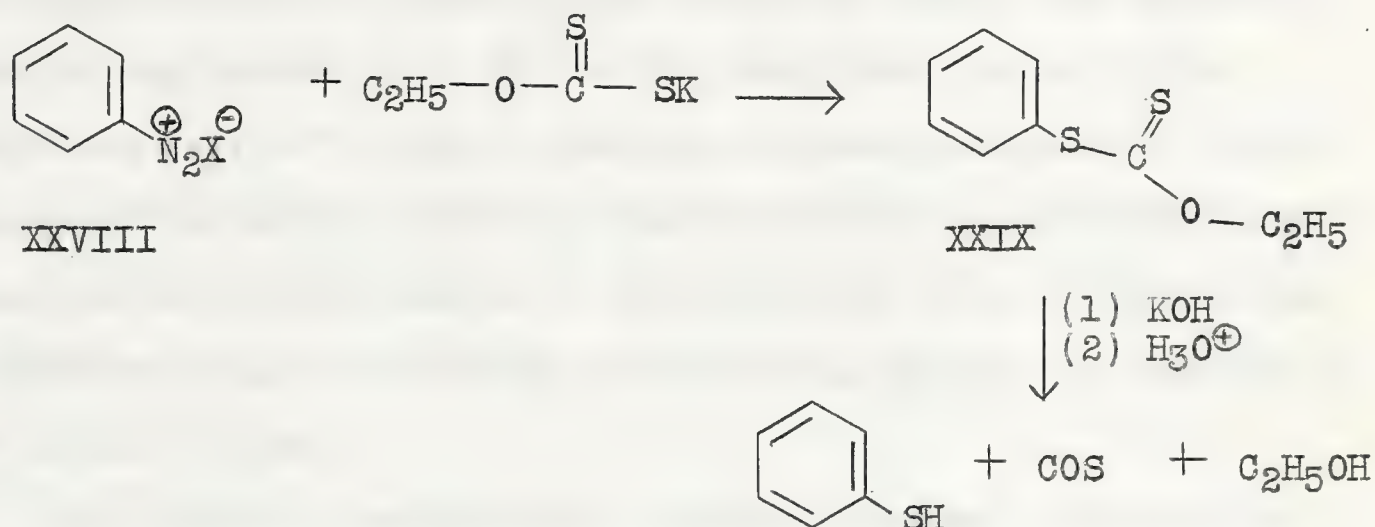
Employing this method, Phillips and Shapiro (33) converted 2-bromopyridine to 2-mercaptopyridine. Recently, Reynolds and co-workers (34) improved this procedure by preparing the S-alkylthiocarbonium salt in a high boiling solvent, followed by decomposition of this salt by a high boiling amine. The desired thiol was then conveniently separated by direct distillation from the reaction mixture.

It should be emphasized that the above two methods require an alkylating (or arylating) agent which contains a reactive halogen. Simple aromatic halides, in which the halogen is not activated, do not form mercaptans by these procedures. Replacement of the halogen in an aromatic halide by these methods can

be accomplished only if there is present in the molecule an activating moiety, such as an ortho or para nitro group in the benzene ring, or the hetero nitrogen atom in pyridine. Thus, attempts by Haarstad and Brown (35) to directly displace nuclear bromine or chlorine in the benzene-ring portion of indole by the mercapto group by use of potassium hydrosulphide or thiourea in various solvents, were unsuccessful.

The replacement of an amino group by a mercapto group on an aromatic nucleus is effected by treatment of the diazotized amine (XXVIII) with potassium ethyl xanthate, followed by hydrolysis of the intermediate aryl ethyl xanthate (XXIX) (36).

Lithium aluminum hydride

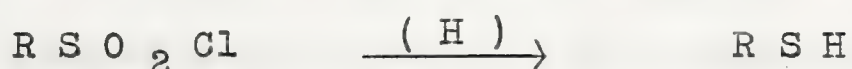


reduction of the xanthogenic esters has improved the thiol yields considerably (37), but this procedure requires isolation of the ester prior to reduction.

Direct application of this method to an aminoindole would subject the indole system to a strongly acidic medium in the diazotization step. Difficulties would therefore arise, since

indoles are known to yield dimeric and trimeric forms upon treatment with strong acids such as hydrochloric, hydrobromic, or phosphoric acids (38, 39).

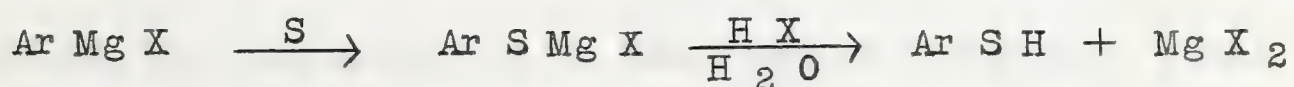
Aryl sulphonyl chlorides have been reduced to the corresponding mercaptans with zinc dust and sulphuric acid (40) or tin and hydrochloric acid (41). Both alkyl and aryl sulphonyl



chlorides, upon treatment with lithium aluminum hydride, afford thiols in 40-50% yield (42).

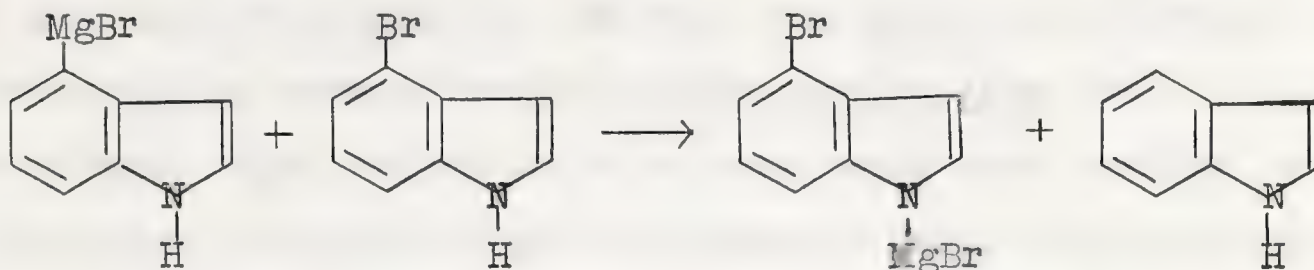
Since direct sulphonation of indole with pyridine-sulphur trioxide complex at temperatures below 50° gives the unstable indole-1-sulphonic acid, while the same reaction at higher temperatures (100°) yields indole-2-sulphonic acid (43), application of the above method in the preparation of mercaptoindoles would involve introduction of the sulphonic acid grouping into an appropriately substituted benzene-ring before cyclization to the indole system.

The action of sulphur on a Grignard reagent, followed by hydrolysis, also results in the formation of mercapto compounds (44, 45).



Since indoles react with Grignard reagents to form indolyl-magnesium halides (46), this reaction would not be directly applicable to the synthesis of mercaptoindoles. Attempted form-

ation of the Grignard reagent from 4-bromoindole, for example, would be complicated by reactions such as the one shown below.



Hence, one could not selectively replace, via Grignard preparation, the halogen atom in 4-, 5-, 6-, or 7-haloindoles by the mercapto group.

Although many of the methods described above are not directly applicable to the synthesis of mercaptoindoles, it should be noted that they could indeed be employed to prepare a sulphur-containing aromatic compound which could then be cyclized to the corresponding indole.

3. Previous Work on the Synthesis of Mercaptoindoles.

Although a synthesis of the 2- and 3-mercaptoindoles was reported by Oddo and Mingoa in 1932 (3), the discussion here will be limited to the previous work concerning the preparation of the benzene-ring substituted mercaptoindoles.

In the foregoing section concerning the methods of preparation of indoles and mercaptans, it was noted that a number of the methods described had been used in attempts to prepare mercaptoindoles, but had proved to be unsuccessful. However, since several methoxy-o-nitrotoluenes had been successfully condensed with ethyl oxalate and then cyclized to the corresponding methoxyindoles (29) via the Reissert procedure (25), Haarstad and Brown

(35) investigated a similar approach for the synthesis of benzene-ring substituted mercaptoindoles, which involved the introduction of the sulphur moiety, in the form of a protected thioether, into a substituted benzene nucleus before cyclization to the indole structure. Application of this route would then involve, in the final step, cleavage of the thioether in order to produce the free mercaptoindole. Therefore, the choice of the benzylthioether as the sulphur-containing group appeared to be advantageous, since benzyl phenyl thioether had been successfully cleaved with sodium to give a good yield of thiophenol (47). Furthermore, du Vigneaud and co-workers reported facile debenzylation of S-benzylcysteine by sodium in liquid ammonia (48).

This route was successfully applied by Haarstad and Brown to the synthesis of 5- and 6-mercaptoindoles (35). Thus, 2-nitro-*p*-toluidine (XXX) was diazotized and converted to the xanthogenic ester (XXXI) by means of potassium ethyl xanthate. Hydrolysis of the ester by ethanolic sodium hydroxide produced the sodium salt of 4-mercapto-2-nitrotoluene (XXXII) which was immediately benzylated to prevent oxidation to the corresponding disulphide. The resulting 4-benzylthio-2-nitrotoluene (XXXIII), when treated with ethyl oxalate under basic conditions, afforded 4-benzylthio-2-nitrophenylpyruvic acid (XXXIV) which, upon reductive cyclization with ferrous sulphate and ammonium hydroxide, yielded 6-benzylthioindole-2-carboxylic acid (XXXV). Copper chromite catalyzed decarboxylation of the acid in quinoline produced 6-benzylthioindole (XXXVI). Reductive cleavage of the thioether by sodium in liquid ammonia afforded 6-mercaptoindole (XXXVII).

The 5-mercaptoindole was prepared by an analogous route to that described above (35).

Continuing this work, Cushley and Brown (49) proposed a similar route for the preparation of the 4- and 7-mercaptoindoles.

In attempts to synthesize the compound 6-nitro-o-toluidine, which was required for preparation of 6-benzylthio-2-nitrotoluene via the route indicated above, Cushley (49) found that published procedures gave unsatisfactory results. Thus, selective reduction of trinitrotoluene, reported to give 4-amino-2,6-dinitrotoluene (50), produced a substance which could be deaminated (51) only in very low yield. The crude 2,6-dinitrotoluene obtained from this reaction failed to reduce satisfactorily to 6-nitro-o-toluidine either with ammonium sulphide (52) or by electrolytic means (53).

A more direct route to 6-benzylthio-2-nitrotoluene, the precursor of 4-mercaptoindole in the Reissert synthesis, became available when it was found (49) that potassium benzyl mercaptide, a more nucleophilic reagent than potassium hydrosulphide (54), successfully displaced the halogen of 6-bromo-2-nitrotoluene, especially if the reaction was carried out in dimethylformamide (55), thus affording the desired thioether in 40% yield.

By subjecting the 6-benzylthio-2-nitrotoluene to a modified Reissert synthesis, Cushley (49) was able to obtain 4-benzylthioindole-2-carboxylic acid. However, attempted decarboxylation of this acid by usual procedures proved to be unsatisfactory and he was unable to isolate pure 4-benzylthioindole.

Regarding the preparation of 7-mercaptoindole by the route

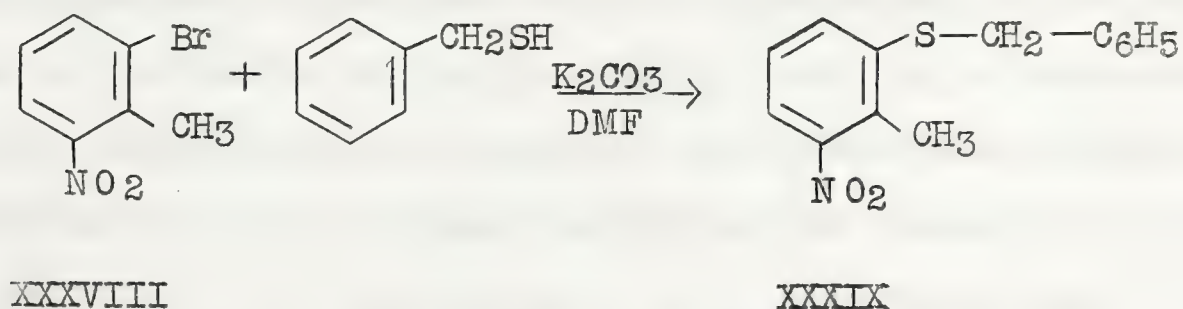
described above, Cushley (49) was able to obtain a small yield of the intermediate 3-benzylthio-2-nitrotoluene by treatment of 3-amino-2-nitrotoluene in a manner analogous to that used by Haarstad and Brown (35) in the synthesis of 4-benzylthio-2-nitrotoluene. However, all attempts to condense the 3-benzylthio-2-nitrotoluene with ethyl oxalate failed. Several condensing agents such as sodium ethoxide, potassium ethoxide, and potassium t-butoxide, were employed in various solvents but no phenylpyruvic acid was isolated.

Therefore, since the total synthesis of all the benzene-ring substituted mercaptoindoles had not yet been accomplished, it was thought desirable to complete the preparation of the remaining unknown indolyl mercaptans, the 7- and especially the 4-mercaptoindole, in order that they might become available for physiological testing.

RESULTS AND DISCUSSION

Although, as noted in the introduction to this work, Cushley and Brown (49) had achieved only limited success in their attempts to prepare the 4- and 7-mercaptoindoles via the Reissert synthesis, it was decided to continue investigation of this general approach. It was hoped that introduction of appropriate modifications to the usual procedures used in the Reissert reaction would result in successful production of the two remaining unknown indolyl mercaptans. Accordingly, the isomeric 3- and 6-benzylthio-2-nitrotoluenes which could then be subjected to an appropriately modified Reissert synthesis to give the 7- and 4-mercaptoindoles respectively, were synthesized.

The intermediate 6-benzylthio-2-nitrotoluene (XXXIX) was prepared in the manner described by Cushley and Brown (49). Thus, displacement of the halogen atom of 6-bromo-2-nitrotoluene (XXXVIII) by treatment with potassium benzyl mercaptide in dimethylformamide, gave the thioether in 26% yield.

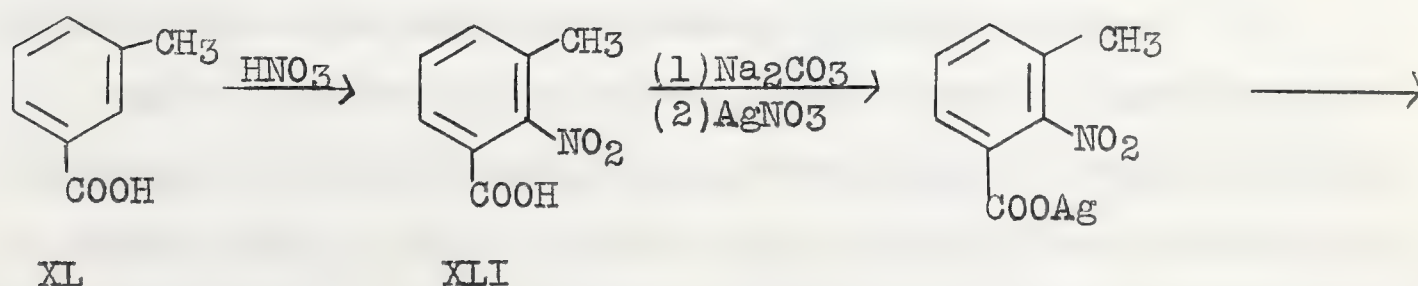


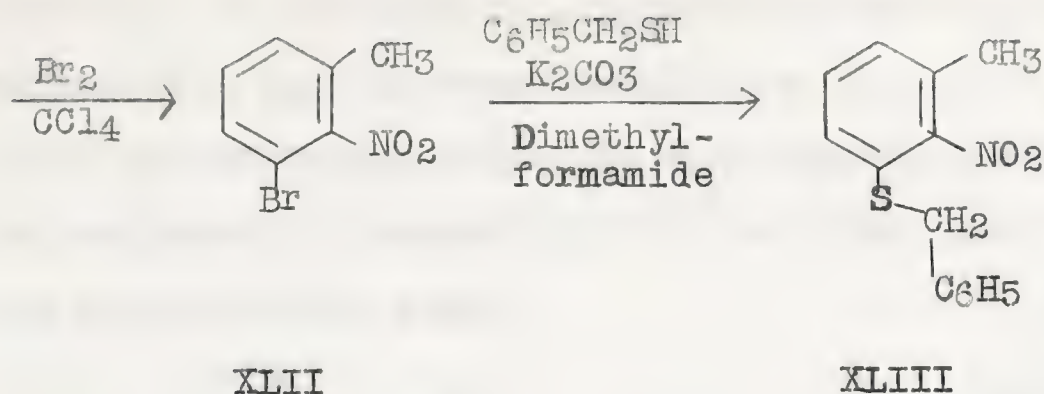
There have been few reports in the literature concerning the preparation of benzyl mercaptan. Märcker (56) first prepared the thiol in 1865 by the action of alcoholic potassium hydrosulphide on benzyl chloride. Reaction of benzyl chloride with sodium thio-

sulphate (57) or of benzyl alcohol with thiourea in the presence of hydrobromic acid (58) also results in the formation of the corresponding mercaptan. Zinner (59), employing an atmosphere of nitrogen or hydrogen sulphide, produced the thiol in 85% yield by causing benzyl bromide to react with potassium hydrosulphide. However, due to the relative ease of isolation and purification of the product, the method of Urquhart and co-workers (60) was adopted in our work. Thus, reaction of benzyl chloride with thiourea, followed by alkaline hydrolysis of the intermediate isothiuronium salt, afforded benzyl mercaptan in 80% yield.

Commercial benzyl mercaptan, which was obtained in the latter stages of this work, was also successfully employed in our reactions.

The precursor to 7-mercaptoindole in the Reissert synthesis, 3-benzylthio-2-nitrotoluene, was obtained by the following route. Nitration of m-toluic acid (XL) by fuming nitric acid (61) gave a 41% yield of 2-nitro-m-toluic acid (XLI), which, by application of the Hunsdiecker reaction (62, 63), was converted in 49% yield to 3-bromo-2-nitrotoluene (XLII). Replacement of the halogen atom of the latter by the benzylthio group in an analogous manner to that employed in the synthesis of 6-benzylthio-2-nitrotoluene, gave the desired thioether (XLIII) in 86% yield.





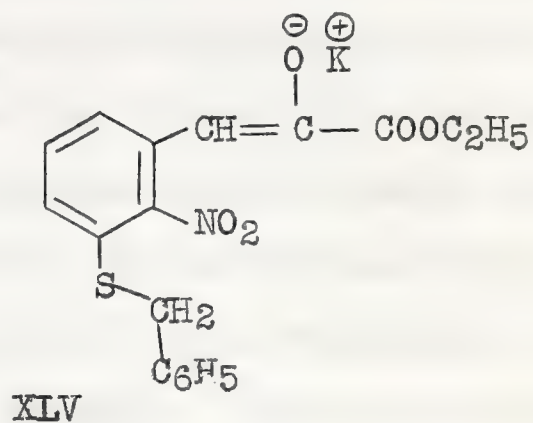
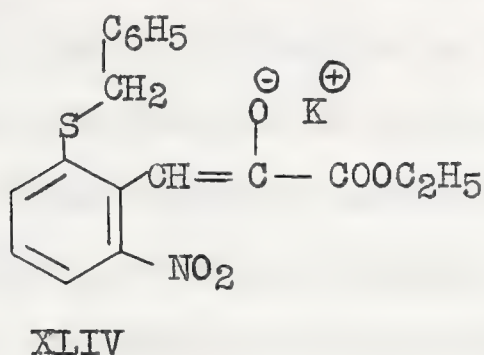
The next step in the Reissert indole synthesis involved the base-promoted condensation of the substituted toluenes with ethyl oxalate.

Although the use of sodium ethoxide as condensing agent and ethanol as solvent was found to be quite satisfactory for the Reissert condensation of both the 4- and 5-benzylthio-2-nitrotoluenes (35), application of these conditions to the 3- and 6-benzylthio-2-nitrotoluenes gave only negligible amounts of the corresponding pyruvates. Accordingly, other conditions were sought which would effect these condensations.

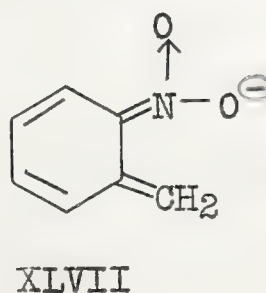
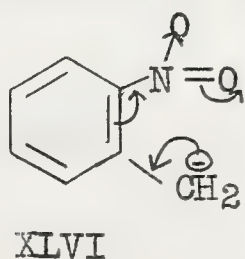
In 1924, Wislicenus and Thoma (26) reported that the use of potassium ethoxide as base, instead of the usual sodium ethoxide, as well as replacement of the usual alcohol solvent by anhydrous ether, resulted in much improved yields in the Reissert reaction. More recently, Snyder and co-workers (64) employed this technique to obtain a nearly quantitative yield of 5-bromo-2-nitrophenylpyruvic acid from the corresponding o-nitrotoluene.

Application of these reaction conditions to the 3- and 6-benzylthio-2-nitrotoluenes, along with extended reaction times of several days at room temperature, permitted the isolation of the potassium enolates of ethyl 3- and 6-benzylthio-2-nitrophenyl-

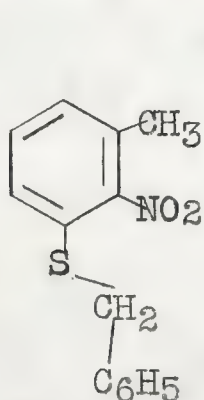
pyruvate. The 6-benzylthio-2-nitrotoluene required, at the maximum, six days at room temperature to produce the enolate (XLIV) in 94% yield, while the 3-benzylthio-2-nitrotoluene gave the condensation product (XLV) in only 68% yield even after sixteen days reaction time.



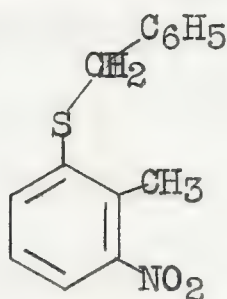
The greater difficulty the 3- and 6-benzylthio-2-nitrotoluenes find in undergoing the Reissert condensation, as compared with the 4- and 5- isomers, might be attributed to the lower degree of activation which the methyl groups experience due to the ortho nitro groups. The requirement of a strong activating group in this reaction was shown by Reissert (25), who found that although the o- and p-nitrotoluenes, in which the nitro groups are in direct conjugation with the methyl groups, could readily be condensed with ethyl oxalate to give the corresponding pyruvic acids, m-nitrotoluene failed to undergo this transformation. It would thus appear likely that the benzylic carbanion (XLVI), which must be formed in the reaction in order to effect condensation, is stabilized by resonance with the ortho nitro group. The contributing structure (XLVII) would then involve coplanarity of the nitro group with the ring.



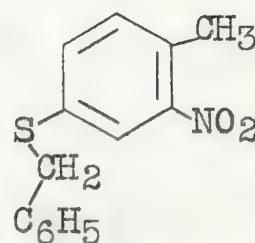
If coplanarity of the nitro group with the benzene ring is responsible, at least in part, for the activation of the methyl group and subsequent removal of a proton by base to form the carbanion, it is readily seen that the groups in the two positions ortho to the nitro substituent in 3-benzylthio-2-nitrotoluene (XLI^{III}) and the buttressing effect of the benzylthio group upon the methyl substituent in the 6-benzylthio-2-nitrotoluene (XXXIX) would indeed cause a marked restriction to the coplanarity of the nitro group with the ring as compared with that attainable in the 4- (or 5-)benzylthio-2-nitrotoluene (XXXIII). In support of this view, it has been found (49) that the position of the characteristic absorption bands in the infrared spectrum of the nitro group in these nitrotoluenes resemble those for the aliphatic nitro group in nitromethane to a progressively greater degree in the order 3-benzylthio-2-nitrotoluene > 6-benzylthio-2-nitrotoluene > 4-benzylthio-2-nitrotoluene (see Table I). The order of apparent ease of condensation of these toluides with ethyl oxalate is 4-benzylthio-2-nitrotoluene > 6-benzylthio-2-nitrotoluene > 3-benzylthio-2-nitrotoluene.



XLI^{III}



XXXIX



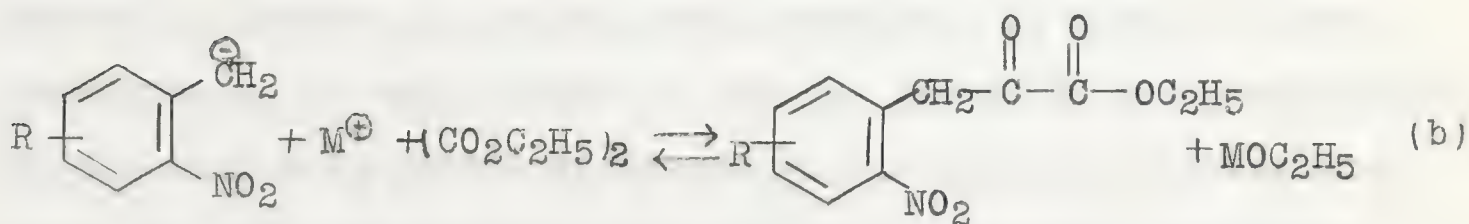
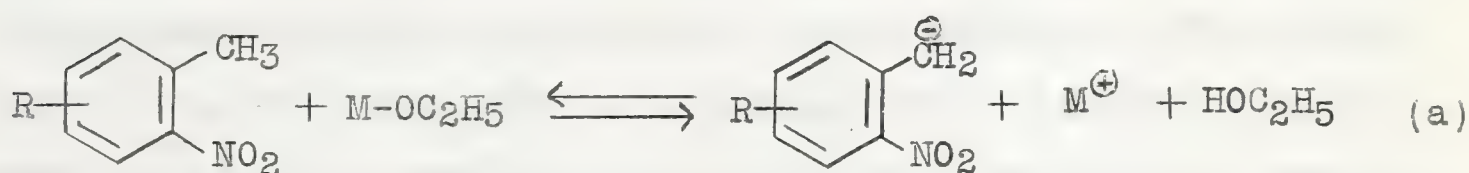
XXXIII

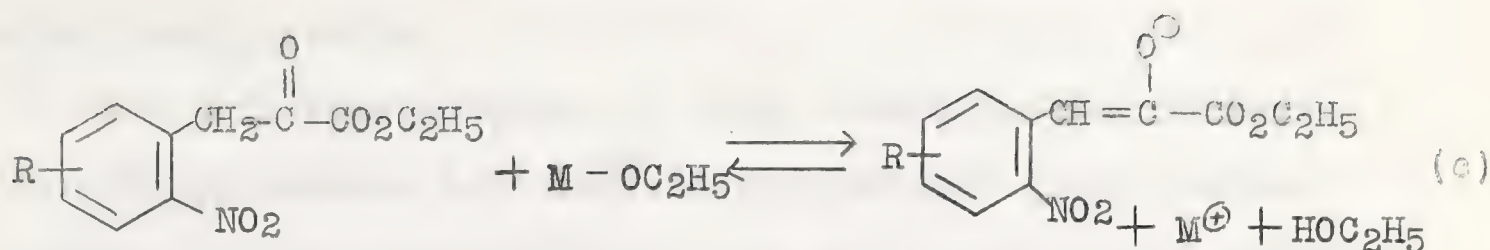
TABLE I

Stretching Bands of the Nitro Group in the Infrared
(Calibrated with polystyrene, 6.238μ)

Compound	Stretching Bands, μ	
	Asymmetric	Symmetric
<i>o</i> -Nitrotoluene	6.54	7.40
4-Benzylthio-2-nitrotoluene	6.53	7.40
6-Benzylthio-2-nitrotoluene	6.52	7.37
3-Benzylthio-2-nitrotoluene	6.50	7.29
Nitromethane	6.38	7.18

It is also possible that the greater difficulty in the formation of the pyruvates in the case of the 3- and 6-benzylthio-2-nitrotoluenes than for the 4- and 5- isomers may be due, at least in part, to an unfavorable shift in the equilibria indicated below.





The requirement of a stronger base, such as potassium ethoxide, to shift the equilibrium to the right in equation (a), as well as application of ether as solvent, which causes precipitation of the enolate (step c) is therefore understandable. It should be noted, however, that the relative solubilities of the enolate products might also partly account for the order of apparent ease of condensation of these nitrotoluenes, since in our work, product yield alone indicates the overall ease of condensation.

It was found that in attempts at converting the potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate to the pyruvic acid by hydrolysis with aqueous base, some 6-benzylthio-2-nitrotoluene was obtained. Furthermore, when pure 4-benzylthio-2-nitrophenylpyruvic acid was left in a solution of 95% ethanol (from which the acid could be crystallized) for a period of four weeks at room temperature, the bulk of the pyruvic acid reverted to the corresponding toluene, a fact clearly demonstrating the reversible nature of the Reissert reaction. In view of these observations, it was decided to use the potassium enolates directly for the next step in the synthesis of the indoles, a procedure which had been successfully employed by Snyder and co-workers (64) in the case of the potassium enolate of ethyl 5-bromo-2-

nitrophenylpyruvate.

The potassium enolates of ethyl 3-(and 6-)benzylthio-2-nitrophenylpyruvate were reductively cyclized using ferrous sulphate and ammonium hydroxide (29, 65). Since both pyruvates were relatively insoluble in cold aqueous medium, best results were obtained when a hot solution of the salt in dilute ammonium hydroxide was added to a boiling suspension of ferrous hydroxide, thus also ensuring an excess of reducing agent throughout the reaction. It was found that the resulting indole-2-carboxylic acids were strongly adsorbed on the ferric oxide sludges obtained from the reduction mixtures and could be isolated only by repeated extraction of the respective sludges with boiling dilute ammonium hydroxide.

Decarboxylation of the 4- and 7-benzylthioindole-2-carboxylic acids by usual procedures proved to be very difficult.

A number of methods have been employed to remove carbon dioxide from various substituted indole-2-carboxylic acids. Decarboxylations have been accomplished in the case of the 4-, 5-, 6-, and 7-fluoroindole-2-carboxylic acids, in yields of 80, 52, 51, and 48% respectively, by simply heating the substances above their melting points (66). The 4- and 6-chloroindole-2-carboxylic acids required more vigorous treatment, but readily gave the decarboxylated products in 73 to 78% yield when they were heated with cuprous chloride in refluxing quinoline (67, 68). However, Barltrop and Taylor (69) were unsuccessful in their attempts to remove the carboxyl group from 4- or 6-bromoindole-2-carboxylic acid by heating these compounds in refluxing quino-

line with or without catalysts such as cuprous bromide, cupric oxide, or copper powder.

The variable and frequently poor results obtained in decarboxylation of the benzene-ring halogenated indole acids by Uhle's method (67, 68) which involved heating the acids with cuprous chloride in refluxing quinoline, was found by Rydon and Tweddle (65) to be due to contamination of the acids by sulphate ion, stemming from the preceding ferrous ammonium sulphate cyclization step. These authors, after repeated washing of the acids with water to eliminate the sulphate ion, replaced the usual cuprous chloride catalyst by copper chromite and were thus able to obtain consistently good yields of the 4-, 5-, 6- and 7-chloro-indoles from the corresponding indole-2-carboxylic acids.

Plieninger et. al. (70) reported 60% yields of the 4- and 6-bromoindoles from the corresponding indole-2-carboxylic acids by mixing the latter with molten cuprous bromide followed by heating the fusion mixture in refluxing quinoline. Snyder and co-workers (64) obtained a 21-24% yield of 5-bromoindole by heating 5-bromoindole-2-carboxylic acid with a mixture of copper bronze and copper chromite, but only a very small yield of product when they attempted to decarboxylate the ammonium salt of the acid in glycerol.

The successful removal of carbon dioxide from 5-iodoindole-2-carboxylic acid (71) by the quinoline-copper chromite procedure of Rydon and Tweddle (65) indicated that this was the most generally satisfactory method reported in the literature for the decarboxylation of substituted indole-2-carboxylic acids. However,

when this method was applied to the 4- and 7-benzylthioindole-2-carboxylic acids, it was found that the acids were decarboxylated in very poor yield with simultaneous loss of some of the sulphur as hydrogen sulphide. Apparently decomposition of the compounds had occurred under these conditions. Accordingly, a route was sought which would provide not only improved yields, but also avoid loss of substituent in the case of the more sensitive sulphur-containing compounds.

It has long been known that a carboxylic acid, heated with catalytic amounts of its copper salt, undergoes facile decarboxylation. Thus, Dougherty (72) was able to obtain an 84% yield of benzophenone by heating o-benzoylbenzoic acid with a small amount of its copper salt. Application of this method to the decarboxylation of the 4- and 7-benzylthioindole-2-carboxylic acids in hot quinoline, resulted in a marked improvement in yields (80 and 85%, respectively). Furthermore, the thioether linkages were not destroyed during the reaction.

In order to determine whether this method was of general applicability in the decarboxylation of indole acids, a number of indole-2-(and -3-)carboxylic acids, which were available in this laboratory, were subjected to this reaction. The results showed that, in general, temperatures necessary to effect elimination of carbon dioxide were lower, and the times required to complete the reaction were far less, than those found for other methods employed. Furthermore, the yields of the decarboxylated products were, in every case, considerably higher than those achieved by the copper chromite-quinoline method. This procedure,

therefore, appears to be of wider applicability than those previously reported in the literature. A summary of the results is given in Table II in which the copper chromite and copper salt methods are compared.

The final step in the preparation of the 4- and 7-mercaptoindoles involved debenzylation of the corresponding benzylthio-^{metal}indoles. Hughes and Thompson (73) reported that alkali_{metal} cleavage of thioethers is accomplished as easily as is cleavage of oxygen ethers with acid, a fact no doubt due to the ability of sulphur to accommodate extra electrons in its outer shell, giving rise to R_2S^- or $R_2S^=$ species, which then dissociate.

Since du Vigneaud and co-workers (48), successfully prepared cysteine from S-benzylcysteine by reductive cleavage of the thioether by sodium in liquid ammonia, their method was adopted. Treatment of a liquid ammonia solution of 4-benzylthioindole with small pieces of sodium, followed by isolation and purification of the crude product, afforded a 68% yield of 4-mercaptoindole. The substance was an oil at room temperature, but could readily be crystallized from Skellysolve B at dry ice temperatures. Similarly, 7-mercaptoindole was obtained in 87% yield from the corresponding 7-benzylthioindole. In each case, a positive Ehrlich test (74), along with infrared and analytical data, showed that the compound was indeed the 4-(or 7-)mercaptoindole.

The overall yield of 4-mercaptoindole in the synthesis described above, was 7.5% starting from the 6-bromo-2-nitrotoluene. Similarly, the 7-mercaptoindole was obtained in 13% yield from 3-bromo-2-nitrotoluene.

TABLE II

The Decarboxylation of Substituted Indole-2-(and -3-)carboxylic Acids

Indole Compound	Reference for Preparation	Method of Decarboxylation	Temperature of Decarboxylation	Time Required (Hours)	Yield of Pure Decarboxylated Product (%)
5-Br;2-CO ₂ H	(64)	a	Refluxing quinoline 210-215°	36	22
		b		4	63
6-Br;2-CO ₂ H	(70)	a	Refluxing quinoline 210-220°	36	25
		b		5	74
7-Br;2-CO ₂ H	(63)	a	Refluxing quinoline 215-220°	48	48
		b		5	61
4-C ₆ H ₅ CH ₂ S;2-CO ₂ H	New compound	a	Refluxing quinoline 205-210°	24	Insignificant
		b		2.5	80
7-C ₆ H ₅ CH ₂ S;2-CO ₂ H	New compound	a	Refluxing quinoline 210-215°	24	15
		b		5	85
6-NO ₂ ;3-CO ₂ H	(77)	c	145-150°	3	90
		b	125-130°	1.5	86

(a) Method was that devised by Rydon and Tweddle (65), involving refluxing quinoline and copper chromite catalyst.

(b) Method is the present method, involving hot quinoline, the acid, and catalytic amounts of its copper salt.

(c) Method involved heated quinoline with no added catalyst.

The chart below gives a comparison of the melting points of the 4-, 5-, 6-, and 7-mercaptoindoles and their precursors in the Reissert indole synthesis.

Compound	Melting Point ^a
6-Benzylthio-2-nitrotoluene ^b	102-103°
5-Benzylthio-2-nitrotoluene ^c	55.5-57°
4-Benzylthio-2-nitrotoluene ^c	78°
3-Benzylthio-2-nitrotoluene ^b	53-54°
4-Benzylthioindole-2-carboxylic acid	185-186°
5-Benzylthioindole-2-carboxylic acid	210.5-211.5°
6-Benzylthioindole-2-carboxylic acid	215°
7-Benzylthioindole-2-carboxylic acid	165-166°
4-Benzylthioindole	35-36°
5-Benzylthioindole	74-75°
6-Benzylthioindole	106.5-107°
7-Benzylthioindole	52-53°
4-Mercaptoindole	oil
5-Mercaptoindole	75-76°
6-Mercaptoindole	70-71°
7-Mercaptoindole	57-58°

a. The melting points of the 4- and 5-benzylthio-2-nitrotoluenes and of the 5- and 6- substituted indoles were taken from reference 35.

- b. The 3- and 6-benzylthio-2-nitrotoluenes were prepared from the 3- and 6-bromo-2-nitrotoluenes respectively, by treatment of the latter with potassium benzyl mercaptide in dimethylformamide (see page 33 of this thesis).
- c. The 4- and 5-benzylthio-2-nitrotoluenes were prepared previously by Haarstad and Brown (see reference 35). Thus, treatment of diazotized 2-nitro-p-toluidine with potassium ethyl xanthate, followed by basic hydrolysis of the xanthogenic ester gave 4-mercapto-2-nitrotoluene which was then benzylated to afford the 4-benzylthio-2-nitrotoluene. Similarly, 6-nitro-m-toluidine was converted to 5-benzylthio-2-nitrotoluene.

EXPERIMENTAL6-Bromo-2-nitrotoluene

Bromination of o-nitrotoluene was carried out by a published procedure (75), as follows. A small amount of bromine was added to a flask containing a mixture of o-nitrotoluene (550 g., 4 moles) and iron filings (10 g.). After the resulting mixture had been warmed on a steam-bath and hydrogen bromide evolution had begun, bromine (720 g., 4.5 moles) was added slowly over a period of 2 hours. When the reaction was nearly complete, the solution was heated on a steam-bath until gas evolution ceased. The cooled material was poured into pentane and the resulting solution washed several times with water, thrice with aqueous sodium bisulphite, and finally with water. After the pentane solution had been dried with anhydrous magnesium sulphate, the solvent was removed, affording a mixture of 6-bromo-2-nitrotoluene and 4-bromo-2-nitrotoluene, which was carefully fractionated under reduced pressure with a meter-length column containing stainless steel packing. The 6-bromo-2-nitrotoluene distilled over first (b.p. 99-102° at 3 mm.) and solidified in the receiver. The next fraction (b.p. 102-108° at 3 mm.), which proved to be a mixture of the two isomers, was kept for later refractionation. The final fraction (b.p. 108-110° at 3 mm.) was pure 4-bromo-2-nitrotoluene, m. p. 46-47°; lit. m. p. 47° (52). Recrystallization of the crude 6-bromo-2-nitrotoluene from ethanol containing a small amount of water gave 225 g. (26%) of pure product, m. p. 41-42°; lit. m. p. 42° (52).

2-Nitro-*m*-toluic Acid

The method of Müller (61) was employed to prepare this compound. Fuming nitric acid (200 ml.) was cooled to 0-5° and *m*-toluic acid (50 g., 0.37 mole) was slowly added. During the course of the reaction, the mixture was stirred constantly and the temperature was kept below 5° by means of external cooling with an ice-water bath. After all the acid had been added, the reaction mixture was stirred at 0-5° for an additional 30 minutes. The solid was collected, washed thoroughly with water, air dried and crystallized from aqueous ethanol, affording 27 g. (41%) of 2-nitro-*m*-toluic acid, m. p. 220-222°; lit. m. p. 219-220° (61).

Silver Salt of 2-Nitro-*m*-toluic Acid

To a solution of 2-nitro-*m*-toluic acid (36.2 g., 0.2 mole) in hot ethanol (400 ml.) was added hot aqueous sodium carbonate (12 g., 0.11 mole, in 100 ml. of water), until the resulting solution was basic. Dilute nitric acid was then added dropwise until the solution was just acid to litmus. Addition of a solution of silver nitrate (34 g., 0.2 mole) in 100 ml. of hot water resulted in the precipitation of the silver salt of 2-nitro-*m*-toluic acid. The white solid was collected by filtration, washed thoroughly, first with water, and then with ethanol and finally air dried. The yield was 49 g. (85%).

3-Bromo-2-nitrotoluene

Published procedures (63) were followed to obtain this compound from 2-nitro-*m*-toluic acid via the Hunsdiecker reaction

(62). Bromine (27 g., 0.17 mole) was added slowly to a stirred suspension of the silver salt of 2-nitro-m-toluic acid (43.5 g., 0.15 mole) in anhydrous carbon tetrachloride (350 ml.) at 25°. The resulting mixture was refluxed for 3 hours, during which time carbon dioxide was evolved. The cooled solution was freed from silver salts by filtration, and the filtrate was washed first with aqueous sodium bisulphite, then with aqueous sodium bicarbonate, and finally with water. Removal of the carbon tetrachloride by distillation afforded a brown oil which, when steam distilled, yielded 16 g. (49%) of 3-bromo-2-nitrotoluene, m. p. 27°; lit. m. p. 27° (76).

Benzyl Mercaptan

The method of Urquhart and co-workers (60) was employed to prepare this compound. Benzyl chloride (63 g., 0.5 mole) and thiourea (39 g., 0.5 mole) were added to 250 ml. of ethanol. The mixture was heated, with stirring, until the substances just dissolved and kept at this temperature for 24 hours. To the cooled reaction mixture was added a solution of 30 g. (0.75 mole) of sodium hydroxide in 300 ml. of water. The reactants were then heated until the precipitate just dissolved and the resulting solution was stirred at this temperature for 6 hours. After the solution was thoroughly cooled and acidified with dilute sulphuric acid, it was extracted thrice with ether. The combined ether extracts were washed twice with water and dried over anhydrous magnesium sulphate. Removal of the ether gave an oil which, upon distillation, afforded 50 g. (80%) of benzyl mercaptan,

b.p. 186-187° at 700 mm.; lit. b.p. 193-195° at 760 mm. (59). In order to prevent oxidation of the product to dibenzyl disulphide, all steps were carried out under an atmosphere of purified nitrogen.

6-Benzylthio-2-nitrotoluene

Powdered potassium carbonate (38.8 g., 0.28 mole) was stirred into 50 ml. of dimethylformamide containing 55 g. (0.25 mole) of 6-bromo-2-nitrotoluene. After addition of benzyl mercaptan (31.3 g., 0.25 mole), the stirred reaction mixture, kept under nitrogen, was heated for 4 hours at 50-55° and then stirred at room temperature for an additional 14 hours. The addition of an equal volume of water, followed by cooling of the reaction mixture to 0°, produced a yellow solid which was collected and triturated, first with dilute sodium hydroxide, and then with water. Crystallization from ethanol gave 17.5 g. (26%) of yellow needles, m. p. 102-103°.

Calc. for $C_{14}H_{13}O_2NS$: C, 64.86; H, 5.02; N, 5.41; S, 12.35.

Found: C, 64.72; H, 5.27; N, 5.38; S, 12.42.

3-Benzylthio-2-nitrotoluene

Following the same procedure outlined above, 17.0 g. (0.079 mole) of 3-bromo-2-nitrotoluene afforded 17.5 g. (86%) of 3-benzylthio-2-nitrotoluene, m. p. 53-54°.

Calc. for $C_{14}H_{13}O_2NS$: C, 64.86; H, 5.02; N, 5.41; S, 12.35.

Found: C, 64.56; H, 5.48; N, 5.27; S, 12.47.

Potassium Enolate of Ethyl 3-Benzylthio-2-nitrophenylpyruvate

Potassium (4.7 g, 0.12 mole) was dissolved in 20 ml. of anhydrous ethanol. To this solution, diluted with 150 ml. of dry ether, was added 17.5 g. (0.12 mole) of ethyl oxalate, followed 15 minutes later by an anhydrous ether solution of 3-benzylthio-2-nitrotoluene (26 g., 0.10 mole). A deep orange solution resulted which, when left at room temperature for 16 days, slowly deposited the potassium enolate as an orange precipitate. The solid, collected and washed thoroughly with anhydrous ether and then air dried, weighed 27.0 g. (68% crude yield). This salt was used directly in the reductive cyclization step.

Potassium Enolate of Ethyl 6-Benzylthio-2-nitrophenylpyruvate

This salt was obtained in 94% yield from 6-benzylthio-2-nitrotoluene by the method described above. The reaction time in this case was 6 days rather than 16.

7-Benzylthioindole-2-carboxylic Acid

For best results, the usual reductive cyclization (36, 52) was modified as follows. A solution of the potassium enolate of ethyl 3-benzylthio-2-nitrophenylpyruvate (10 g., 0.025 mole) in hot (80°) 4N ammonium hydroxide (250 ml.) was added slowly with stirring to a boiling suspension of ferrous hydroxide. (The latter was obtained by the addition of 25 ml. of ammonium hydroxide, $d = 0.90$, to a boiling solution of ferrous sulphate heptahydrate, 45 g., 0.16 mole, in 300 ml. of water.) The resulting mixture was boiled for 90 minutes and then filtered. The ferric

oxide sludge was repeatedly extracted with boiling 2N ammonium hydroxide until acidification of an aliquot of the extract failed to precipitate the indolecarboxylic acid. The combined extracts were cooled to 5°, filtered, and washed several times with ether. Upon acidification of the solution with hydrochloric acid a solid appeared which, when dried, gave 2.2 g. (31%) of 7-benzylthioindole-2-carboxylic acid, m.p. 165-166°.

Calc. for $C_{16}H_{13}O_2NS$: C, 67.84; H, 4.59; N, 4.95; S, 11.31.

Found: C, 67.59; H, 4.75; N, 5.05; S, 11.54.

4-Benzylthioindole-2-carboxylic Acid

This compound was prepared similarly in 56% yield from the potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate. Purification as above gave a brown solid melting at 185-186°.

Calc. for $C_{16}H_{13}O_2NS$: C, 67.84; H, 4.59; N, 4.95; S, 11.31.

Found: C, 67.84; H, 4.63; N, 4.96; S, 11.22.

Copper Salt of 7-Benzylthioindole-2-carboxylic Acid

A stirred mixture of 7-benzylthioindole-2-carboxylic acid (2.83 g., 0.01 mole), sodium carbonate (0.54 g., 0.005 mole), and water (100 ml.) was heated until the acid dissolved. Upon addition of a solution of cupric sulphate pentahydrate (1.26 g., 0.005 mole) in 50 ml. of water, the blue cupric salt of the indole-2-carboxylic acid precipitated. The solid was washed thoroughly with water, air-dried, and then given a final drying in a vacuum desiccator over calcium chloride.

Copper Salt of 4-Benzylthioindole-2-carboxylic Acid

This salt was obtained from 4-benzylthioindole-2-carboxylic acid by the procedure described above.

7-Benzylthioindole

A mixture of 7-benzylthioindole-2-carboxylic acid (2.83 g., 0.01 mole) and its copper salt (0.25 g., 0.0004 mole) in 10 ml. of synthetic quinoline was heated under an atmosphere of nitrogen until carbon dioxide began to evolve. The mixture was kept at this temperature (210-215°) until gas evolution ceased (5 hours). The cooled solution was taken up in ether and the ether solution was washed several times with 1N hydrochloric acid, once with water, twice with dilute sodium carbonate solution, and finally with water. After the ether solution had been dried by anhydrous sodium sulphate, the solvent was removed, affording a solid which, upon crystallization from Skellysolve B, gave 2.05 g. (85%) of 7-benzylthioindole, m. p. 52-53°.

Calc. for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40.

Found: C, 75.36; H, 5.42; N, 5.93; S, 13.71.

4-Benzylthioindole

This compound was prepared from 4-benzylthioindole-2-carboxylic acid as described above. The reaction temperature was 205-210° and the time required to complete the decarboxylation was 2.5 hours. From 2.83 g. (0.01 mole) of the acid was obtained 1.90 g. (80%) of 4-benzylthioindole, m. p. 35-36° (from ethanol).

Calc. for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40.

Found: C, 75.49; H, 5.42; N, 5.98; S, 13.36.

4-Mercaptoindole

Commercial anhydrous liquid ammonia (90 ml.) was placed in an Erlenmeyer flask surrounded by dry ice. After addition of 4-benzylthioindole (3.57 g., 0.015 mole), small pieces of freshly cut sodium metal were stirred into the ammonia until a blue color of 5-10 minutes' duration was obtained. Excess sodium was then destroyed by ammonium chloride, added until the blue color just disappeared. The reaction flask was kept stoppered as much as possible throughout the reaction to minimize absorption of carbon dioxide by the liquid ammonia. The flask was removed from the dry ice and the ammonia driven off under a blanket of purified nitrogen, giving a solid residue which was dissolved in freshly boiled and cooled distilled water. The resulting aqueous solution was washed several times with ether to remove any unreduced material. Acidification at 0° gave a solid which was dried in a desiccator under vacuum over dry calcium chloride. The substance was an oil at room temperature but could readily be crystallized from Skellysolve B at dry ice temperatures. Treatment of a dilute solution of the compound (in ethanol) with one drop of Ehrlich reagent (74) produced a deep violet color characteristic of indoles. Yield 1.5 g. (68%).

Calc. for C_8H_7NS : C, 64.39; H, 4.73; N, 9.39; S, 21.49.

Found: C, 64.37; H, 4.93; N, 9.49; S, 21.08.

7-Mercaptoindole

Debenzylation of 3.3 g. (0.014 mole) of 7-benzylthioindole by the same procedure as described above, gave 1.8 g. (87%) of the pure mercaptan melting at 57-58 ° (from Skellysolve B). This compound also gave a positive Ehrlich test (74).

Calc. for C_8H_7NS : C, 64.39; H, 4.73; N, 9.39; S, 21.49.

Found: C, 64.25; H, 4.69; N, 9.31; S, 21.45.

Physiological Tests with Mercaptoindoles

To date, only 4-mercaptoindole has been tested for anti-carcenogenic properties and these tests have proven negative. Thus, subperitoneal injection of 4-mercaptoindole into rats infected with ascites cells failed to cause any regression. Futher tests with this compound and with the other mercaptoindoles are being carried out by Dr. V. B. Haarstad, New Orleans Medical School, New Orleans, U. S. A..

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PART II

THE REARRANGEMENT

OF

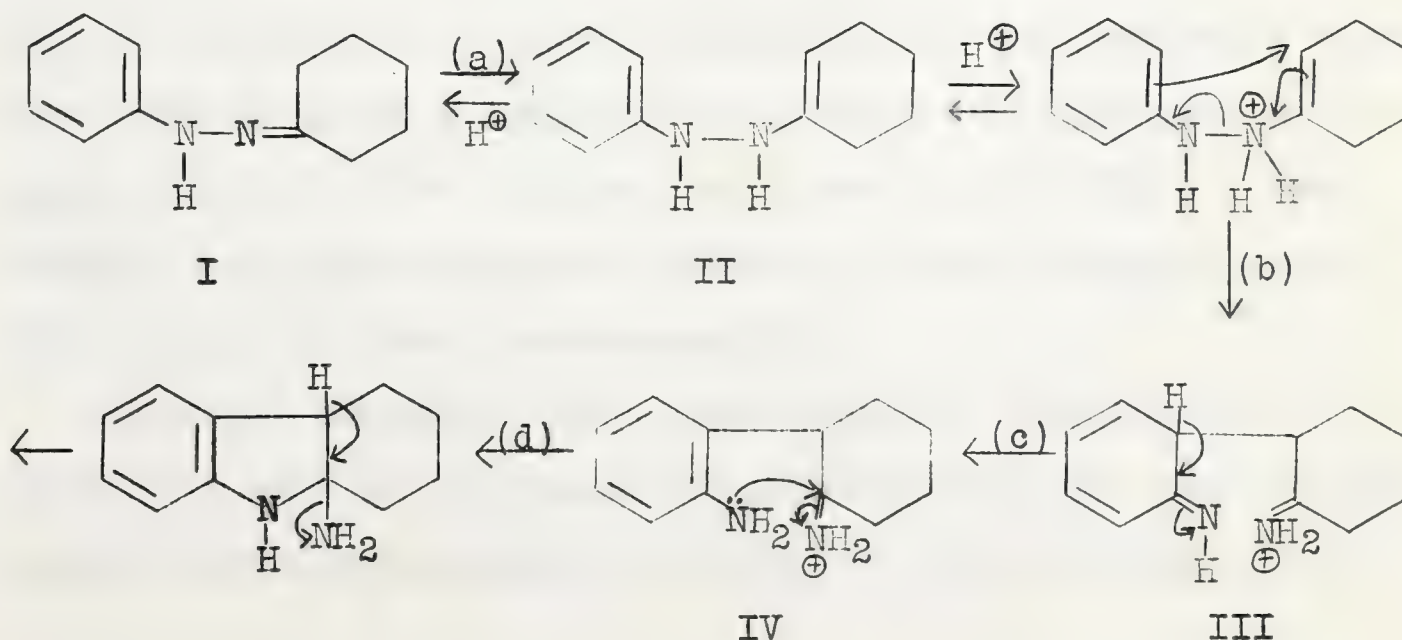
ALLYL 2,6-DIHALOPHENYL ETHERS

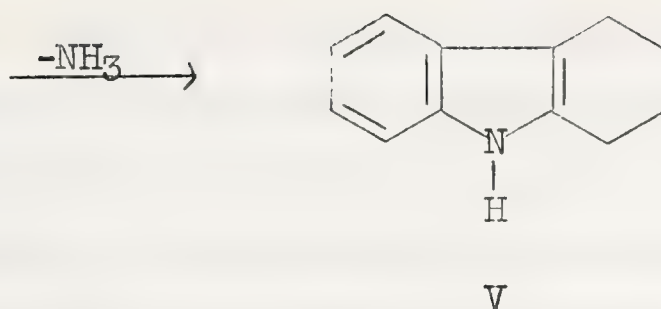
INTRODUCTION

1. The Problem

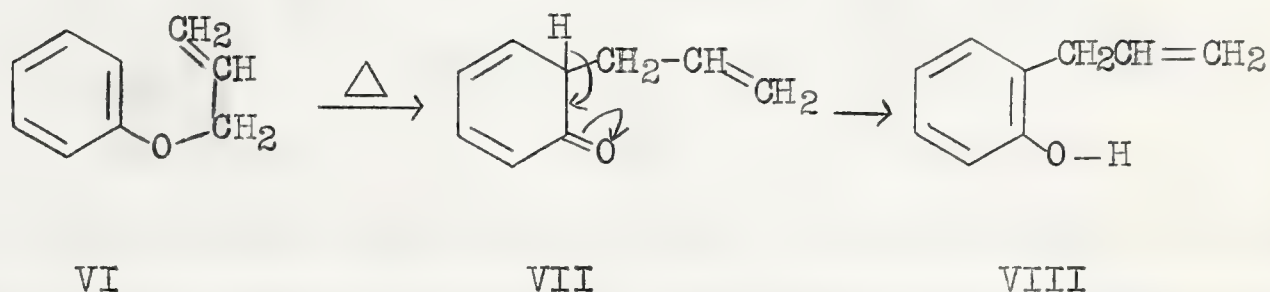
In a paper published some time ago, Carlin and Fisher (1) pointed out the formal analogy which exists between the generally accepted mechanism proposed by Robinson and Robinson (2, 3) for the Fischer indole synthesis and that established to explain the Claisen rearrangement of allyl aryl ethers to the corresponding allylphenols (4-8).

The Fischer reaction involves the cyclization, usually acid catalyzed, of arylhydrazones to the corresponding indoles. The proposed mechanism (2, 3), which can conveniently be illustrated by the ring closure of cyclohexanone phenylhydrazone (I) to 1,2,3,4-tetrahydrocarbazole (V), consists essentially of the following steps: (a) hydrazone-enehydrazine equilibration ($I \rightleftharpoons II$); (b) formation of a new carbon-carbon bond, to give the dienone imine intermediate (III); (c) aromatization ($III \rightarrow IV$); (d) ring closure of IV, followed by loss of ammonia to afford the tetrahydrocarbazole (V).





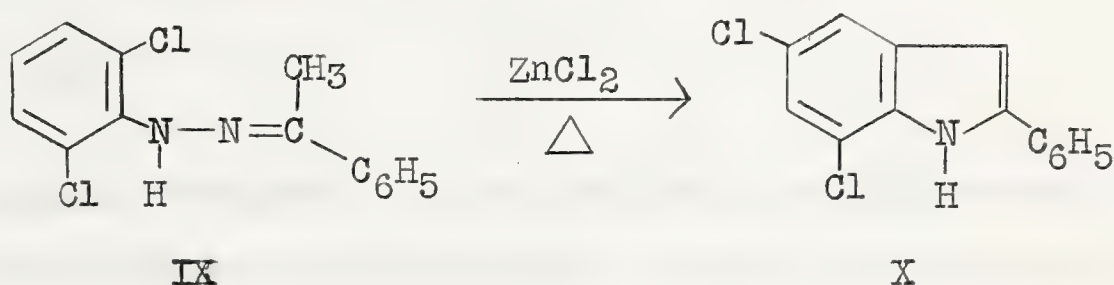
The Claisen rearrangement of an allyl aryl ether which contains at least one unsubstituted ortho position results in the formation of the corresponding o-allylphenol. The generally accepted mechanism (4-8) of this well known thermal rearrangement can be illustrated by the conversion of allyl phenyl ether (VI) to o-allylphenol (VIII), as shown below.



Upon comparison of the two mechanisms described above, it is clearly seen that a distinct analogy exists between steps (b) and (c) of the Fischer indole synthesis and the two steps which have been proposed to explain the Claisen rearrangement to the ortho position. The intermediate dienone imine (III) in the Fischer reaction is formally similar to the proposed dienone (VII) in the Claisen rearrangement.

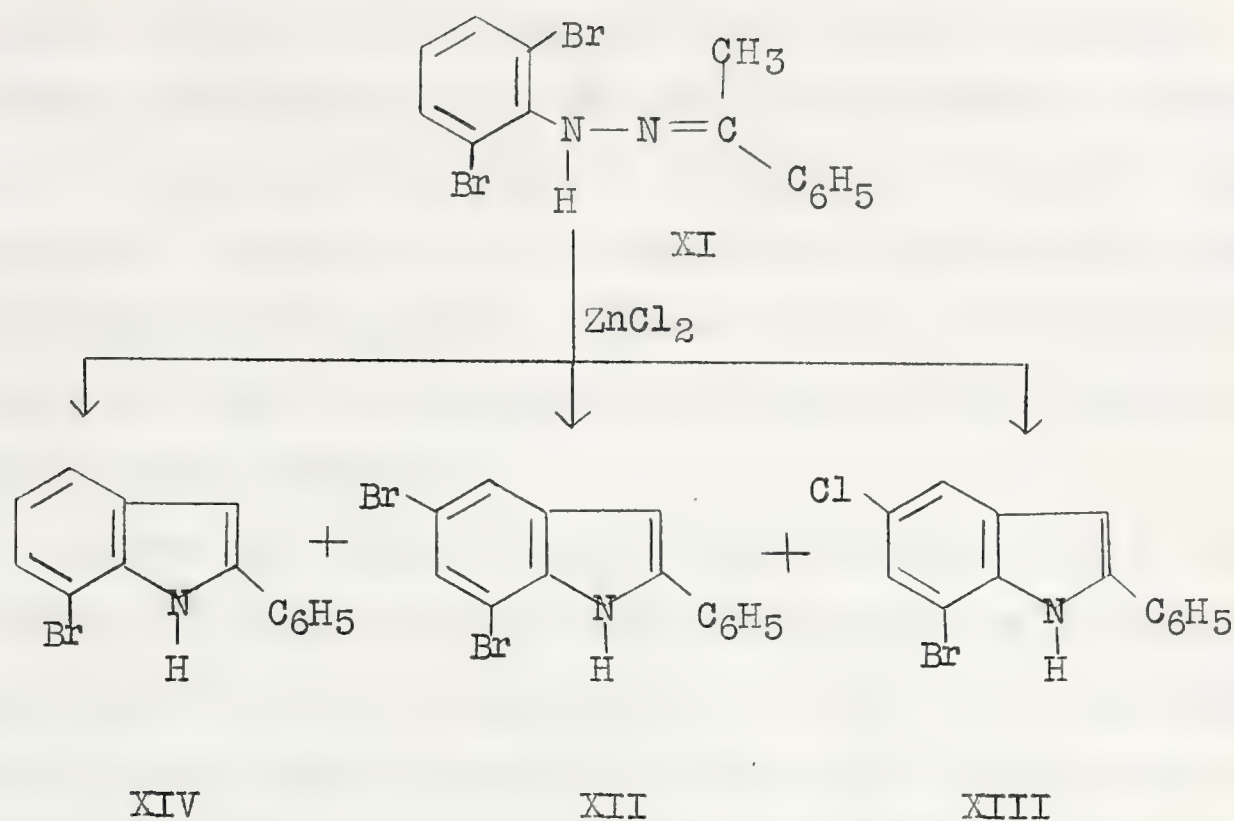
In their original paper concerning the Fischer indole synthesis, Carlin and Fisher (1) reported that the subjection of several 2,6-dichlorophenylhydrazones to the conditions of the

Fischer reaction in the presence of zinc chloride, with or without added solvent, led to the formation of small yields of the corresponding 5,7-dichloroindoles, products which resulted from the migration of one of the chlorine atoms. For example, when acetophenone 2,6-dichlorophenylhydrazone (IX) was heated with zinc chloride in the absence of solvents, or in the presence of nitrobenzene, *o*-nitrotoluene, phenol, or *p*-cresol, the only pure compound recovered from the reaction mixtures was 5,7-dichloro-2-phenylindole (X). The yields of product were generally low (7-25%), and the remaining portions of the reaction mixtures consisted of intractable tars.

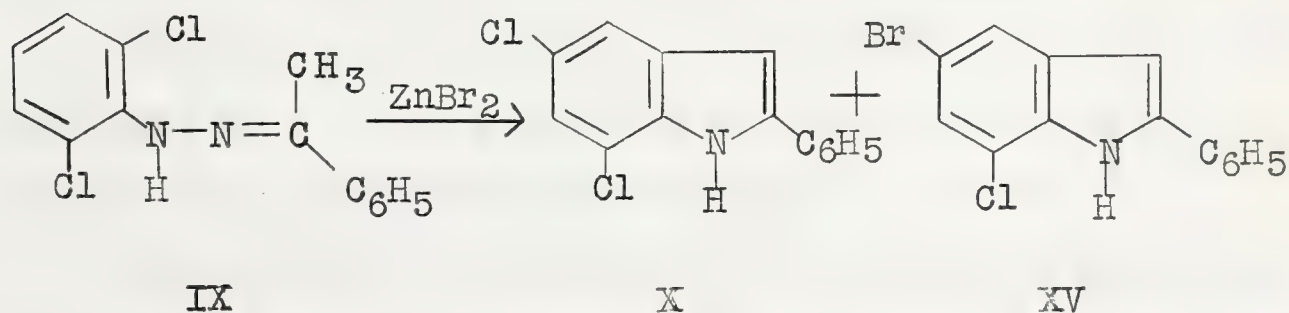


The chlorine migration was shown to occur prior to the formation of the indole ring system, since the products were stable to the reaction conditions employed, and was found to be specific for dichlorophenylhydrazones with a 2,6-orientation of the halogen substituents (1). The products were identified by unambiguous synthesis from the corresponding 2,4-dichlorophenylhydrazones.

Subsequent work by Carlin and Larson (9) showed that upon treatment of acetophenone 2,6-dibromophenylhydrazone (XI) with anhydrous zinc chloride in nitrobenzene at 170-180°, there was formed a mixture containing approximately equimolar amounts of 5,7-dibromo-2-phenylindole (XII) and 7-bromo-5-chloro-2-phenylindole (XIII), along with a trace of 7-bromo-2-phenylindole (XIV).



Similar treatment of acetophenone 2,6-dichlorophenylhydrazone (IX) with anhydrous zinc bromide afforded a mixture of 5,7-dichloro-2-phenylindole (X) and 5-bromo-7-chloro-2-phenylindole (XV), in approximately 1:3 ratio. No monohalogenated indole was found as a product in this case.



These further studies showed that not only halogen migration (to form XII and X), but also halogen exchange (to form XIII and XV) and replacement of halogen by hydrogen (to form XIV) can occur under the appropriate conditions.

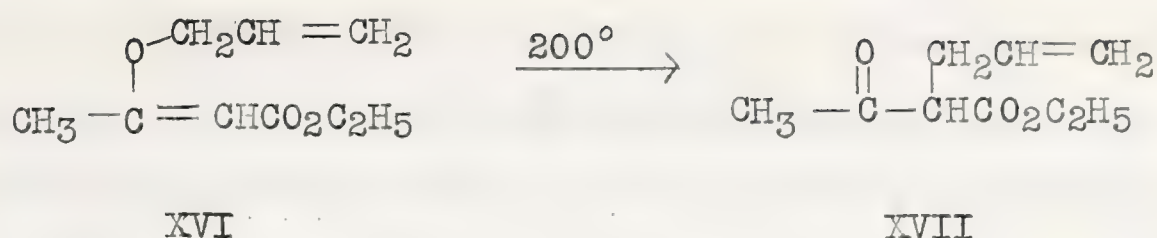
Although, as noted previously, there is a marked similarity between the mechanisms proposed for the Fischer reaction and the Claisen rearrangement, the conversions described by Carlin et. al. (1, 9), and summarized above, concerning the Fischer indole synthesis, appeared to have no recorded analogy among examples of the Claisen rearrangement, although Carlin and Fisher (1) suggested that they might indeed occur but to such a small extent as to have escaped detection.

It was felt that, since the zinc halides appeared to be necessary for the halogen shift and/or exchange in the indole synthesis (1, 9), the application of these Lewis acids might catalyze the Claisen rearrangement as well as bring about similar transformations. Accordingly, it was thought to be of interest to undertake a study of the effect of zinc chloride and zinc bromide on the rearrangement of allyl 2,6-dihalophenyl ethers, as well as to compare the results obtained from these reactions with those from the purely thermal rearrangement of these ethers.

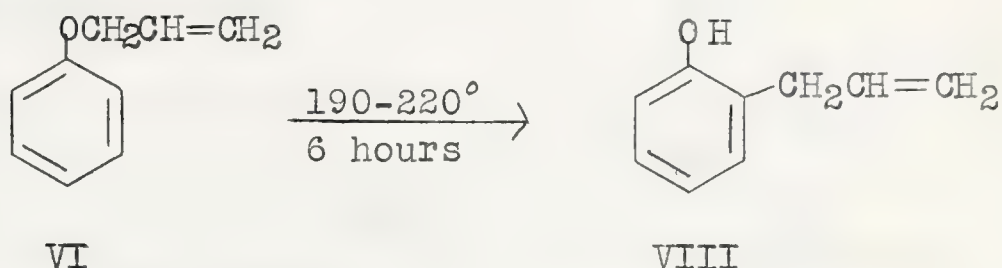
2. General Discussion of the Claisen Rearrangement

Since the work presented in this thesis concerns the Claisen rearrangement, a brief discussion of this reaction may be of assistance in understanding the present problem.

The Claisen rearrangement, which bears the name of its discoverer, was first observed (10) when ethyl O-allylacetoacetate (XVI), upon subjection to distillation at atmospheric pressure in the presence of ammonium chloride, was converted to ethyl α -allylacetoacetate (XVII). Since phenol resembles the



enolic form of acetoacetic ester in acidity, Claisen examined the behavior of allyl phenyl ether (VI) under thermal conditions, and found that it rearranged smoothly at the boiling point to afford o-allylphenol (VIII) in high yield (11).

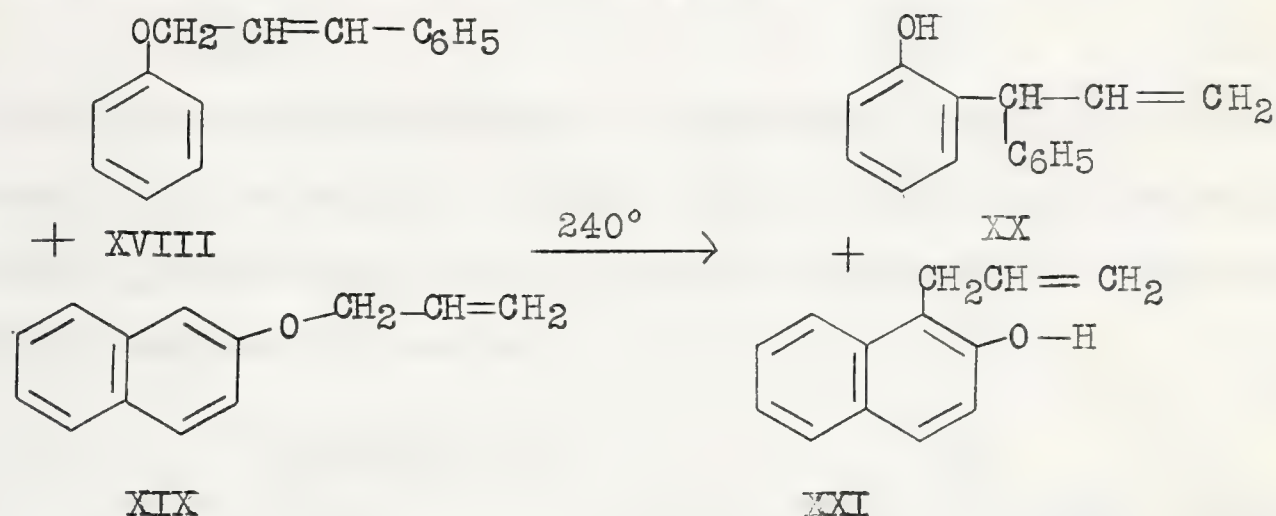


Since its discovery, a great many reports, as well as several reviews (5-8), have appeared in the literature concerning the Claisen rearrangement. Hence, the remainder of the present discussion will be limited to the presentation of a number of the more salient general features of the rearrangement of allyl aryl ethers, along with some specific aspects of the reaction which are directly pertinent to our work.

A. The ortho Claisen Rearrangement

Allyl aryl ethers in which at least one ortho position is unsubstituted, undergo smooth intramolecular rearrangement at high temperatures to yield the corresponding o-allylphenols. This reaction has proven to be quite general and has found many useful applications.

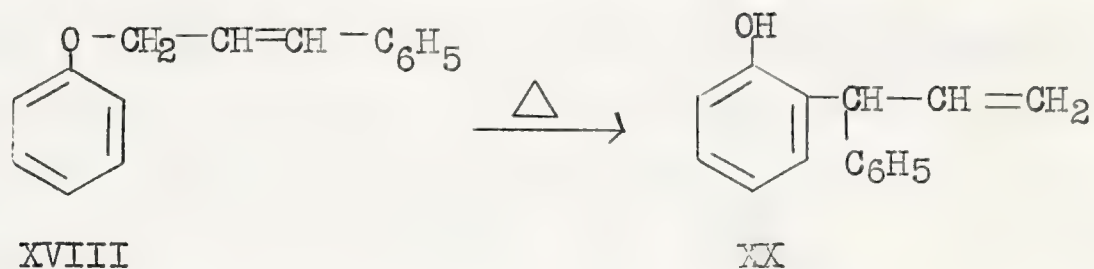
The intramolecular character of this ortho rearrangement has been demonstrated by the absence of cross products when two compounds involving different substituents are allowed to rearrange in the same reaction mixture. Thus, Hurd and Schmerling (12) found that when a mixture of cinnamyl phenyl ether (XVIII) and allyl β -naphthyl ether (XIX) was heated, the only products formed were o-(α -phenylallyl)phenol (XX) and 1-allyl-2-naphthol (XXI). If the reaction were intermolecular, some o-allylphenol would have been formed but this was not observed.



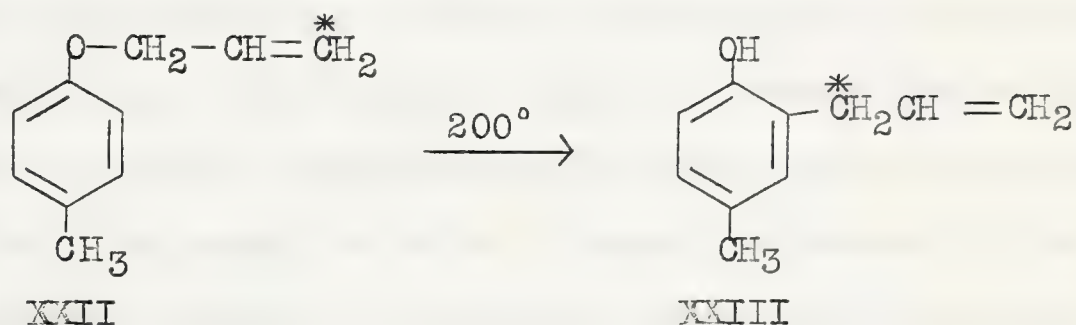
Kincaid and Tarbell (13), in a kinetic study of the rearrangement of allyl p-tolyl ether, found that the reaction was strictly first-order over a fivefold change in concentration in diphenyl ether solution, and that the initial rate in the pure liquid was the same as the rate in diphenyl ether solution. These results also support the conclusion that the rearrangement is intramolecular.

One of the interesting features of the ortho Claisen rearrangement of allyl aryl ethers is the fact that the carbon atom which becomes attached to the aromatic nucleus in the phenolic product, is not the one originally attached to the oxygen atom

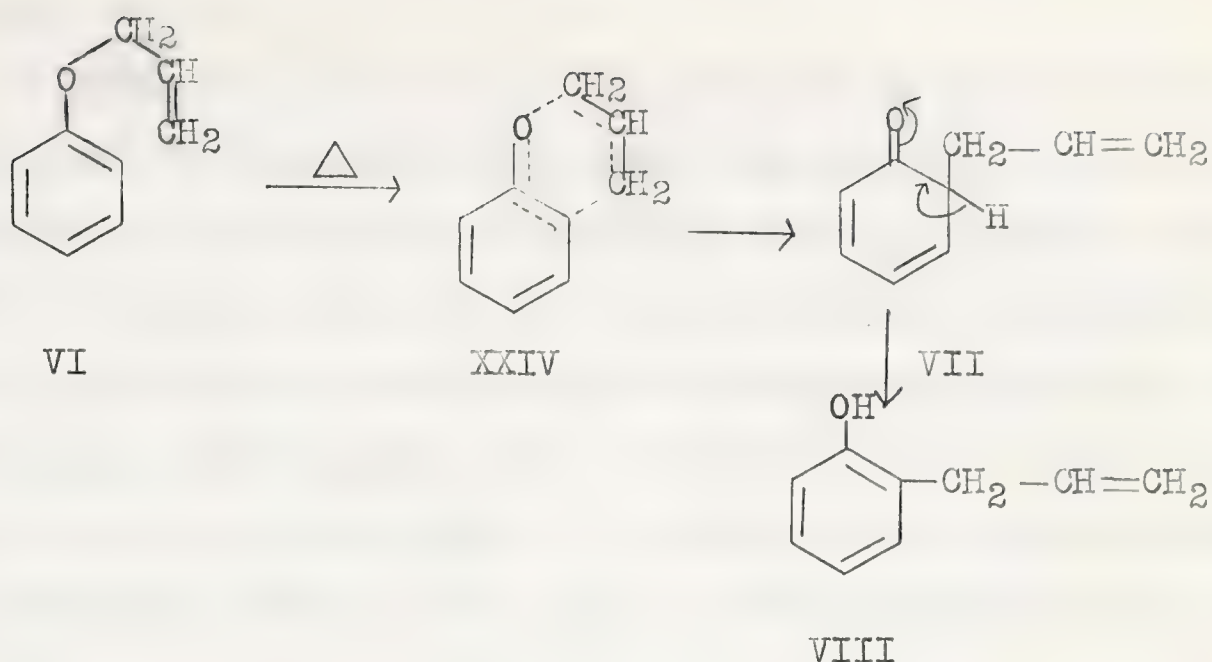
of the ether, but rather the one in the γ -position with respect to the oxygen atom. This inversion of the allyl group, which becomes apparent when substituents are present on either the α - or γ -carbon atom, was first noted by Claisen and Tietze (14) in the rearrangement of cinnamyl phenyl ether (XVIII) to 2-(α -phenylallyl)phenol (XX). More recently, Schmid and Schmid (15) have



illustrated this phenomenon by appropriate labelling of the allyl moiety with radioactive carbon. Thus, rearrangement of allyl-(γ - C^{14}) p-tolyl ether (XXII) afforded 2-allyl(α - C^{14})-p-cresol (XXIII) as the only product.



The above observations, taken as a whole, lend support to the now generally accepted mechanism originally proposed by Hurd and Pollack (4) for the ortho Claisen rearrangement. These authors suggested, as illustrated below, that the rearrangement of, for example, allyl phenyl ether (VI) must proceed through a cyclic transition state (XXIV), giving as the initial reaction product the dienone (VII), which then enolizes rapidly to afford o-allylphenol (VIII) as the final product.



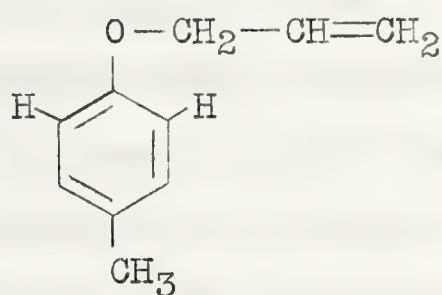
The electronic nature and the stereochemistry of the transition state in the ortho Claisen rearrangement (XXIV) have been the subject of several recent publications. White and co-workers (16-19), as well as Goering and Jacobson (20), have attempted to establish more precisely the degree of bond breaking and bond forming and the amount of ionic character involved in the transition state by investigation of the effect of solvents and substituents on reaction rates. Several research groups (21-26) have been involved in studies to determine the exact geometry of the transition state. Walling and Naiman (27), as well as Brower (28), have attempted to obtain an overall detailed picture of the transition state through measurement of the volume change of activation in the ortho Claisen rearrangement.

Since our work regarding the Claisen rearrangement is concerned primarily with halogen migration in this reaction, and not with the manner in which the allyl migration takes place, the results obtained from the work mentioned above will not be

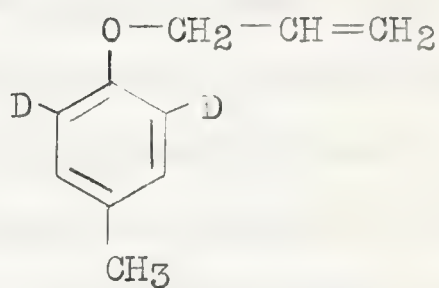
discussed here.

Although the cyclic mechanism detailed above is primarily a description of the reaction and does not take into account the electronic nature and stereochemistry of the transition state (XXIV), it agrees well with the facts known about the rearrangement. The invariable occurrence of inversion of the allyl group in the ortho rearrangement is a necessary result of the cyclic form of the transition state. The first-order reaction kinetics are consistent with the idea that the rate-determining step in the reaction is the transformation of the ether to the dienone intermediate, followed by rapid aromatization to the phenol.

Support for this kinetic pattern of the ortho Claisen rearrangement was presented recently by White and Wolfarth (29), who found that, within experimental error, the rates of rearrangement of allyl p-tolyl ether (XXV) and allyl p-tolyl-2,6-d₂ ether (XXVI) were identical; that is, no isotope effect was operative. These results show that the breaking of the ortho carbon-hydrogen



XXV

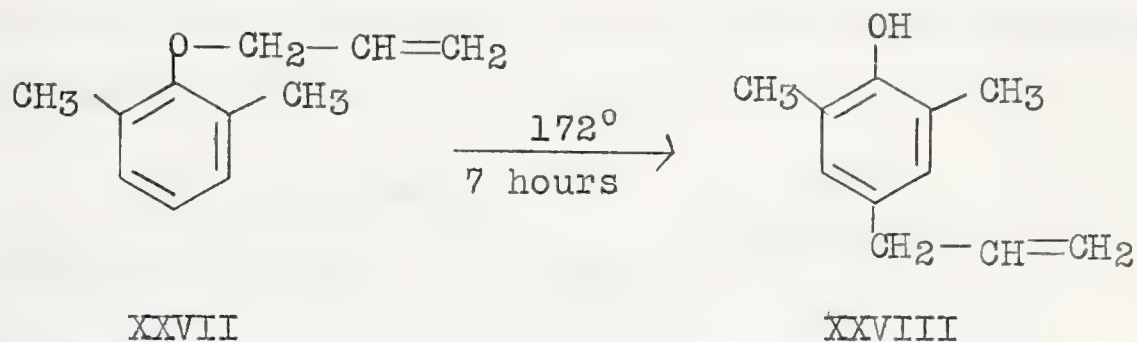


XXVI

bond is not kinetically important, and therefore, that the first step of the rearrangement, involving the conversion of the original ether to the dienone intermediate, is rate-determining.

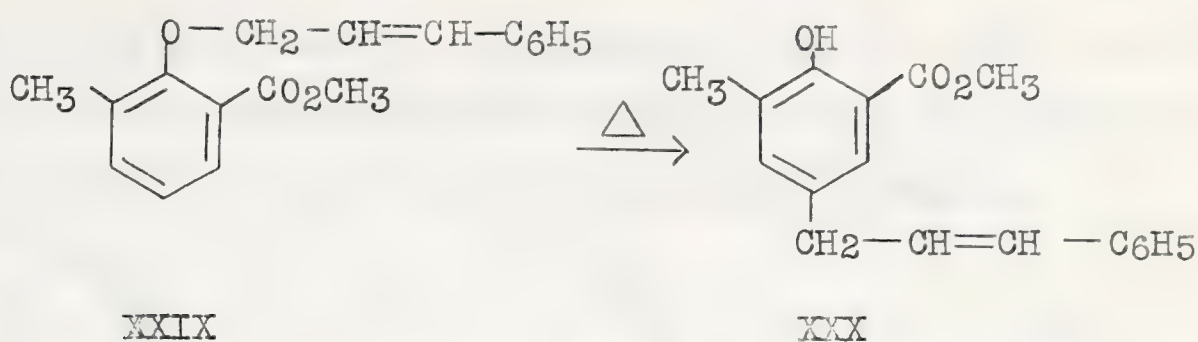
B. The para Claisen Rearrangement

Allyl aryl ethers in which both positions ortho to the ether grouping are substituted, rearrange upon heating to the corresponding p-allylphenol. For example, when allyl 2,6-dimethylphenyl ether (XXVII) is heated at 172° for seven hours in an inert atmosphere, there is formed 4-allyl-2,6-dimethylphenol (XXVIII) in greater than 85% yield (30).

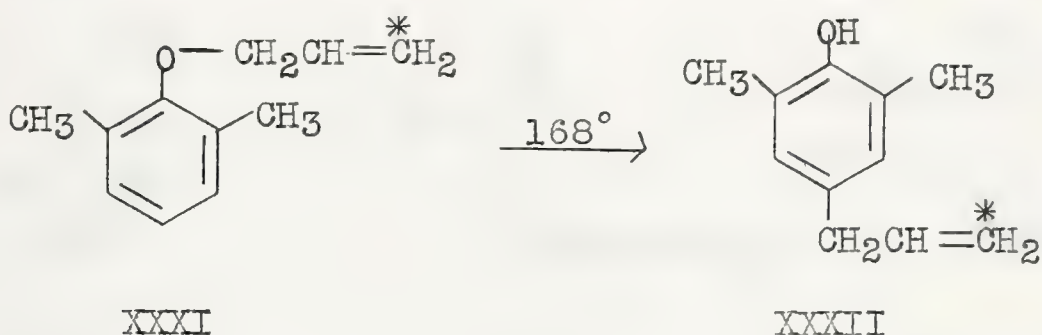


The kinetics of the Claisen rearrangement to the para position are quite similar to those for the ortho rearrangement. Thus, a study of the rearrangement of allyl 2,6-dimethylphenyl ether revealed that the reaction is first-order both in solution and in the pure liquid (30).

Although, as noted previously, the ortho Claisen rearrangement proceeds with inversion of the allyl group, no such final overall interchange is observed in the para rearrangement. That is, in the latter reaction, it is the α -carbon atom of the allyl group in the ether which becomes attached to the benzene nucleus in the resulting p-allylphenol. Thus, for example, cinnamyl 2-carbomethoxy-6-methylphenyl ether (XXIX) rearranges without inversion to yield the p-cinnamyl derivative (XXX) as the sole product (31). A more recent illustration of this non-inversion has been given by Schmid and co-workers (32), who reported that



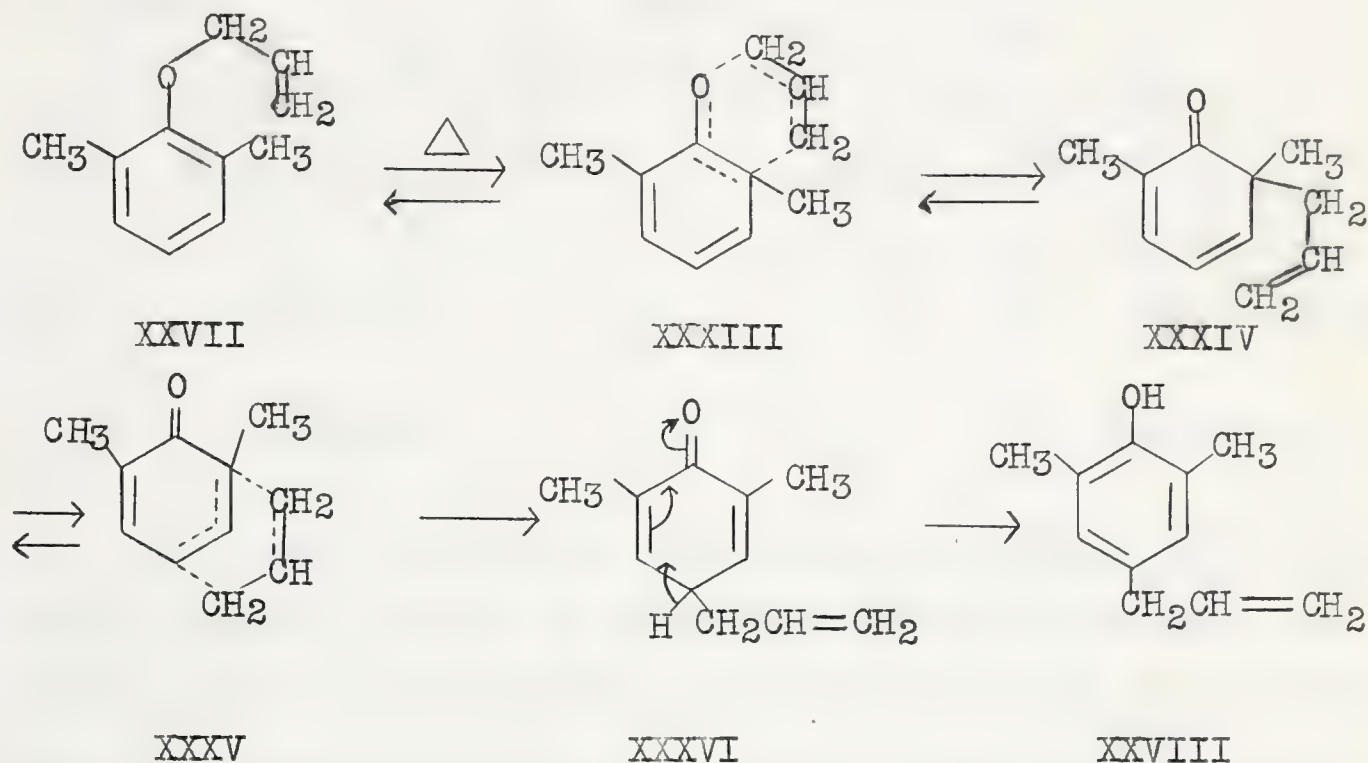
the rearrangement of allyl (γ -C¹⁴) 2,6-dimethylphenyl ether (XXXI) led to the formation of 4-allyl(γ -C¹⁴)-2,6-dimethylphenol (XXXII) in 94% yield.



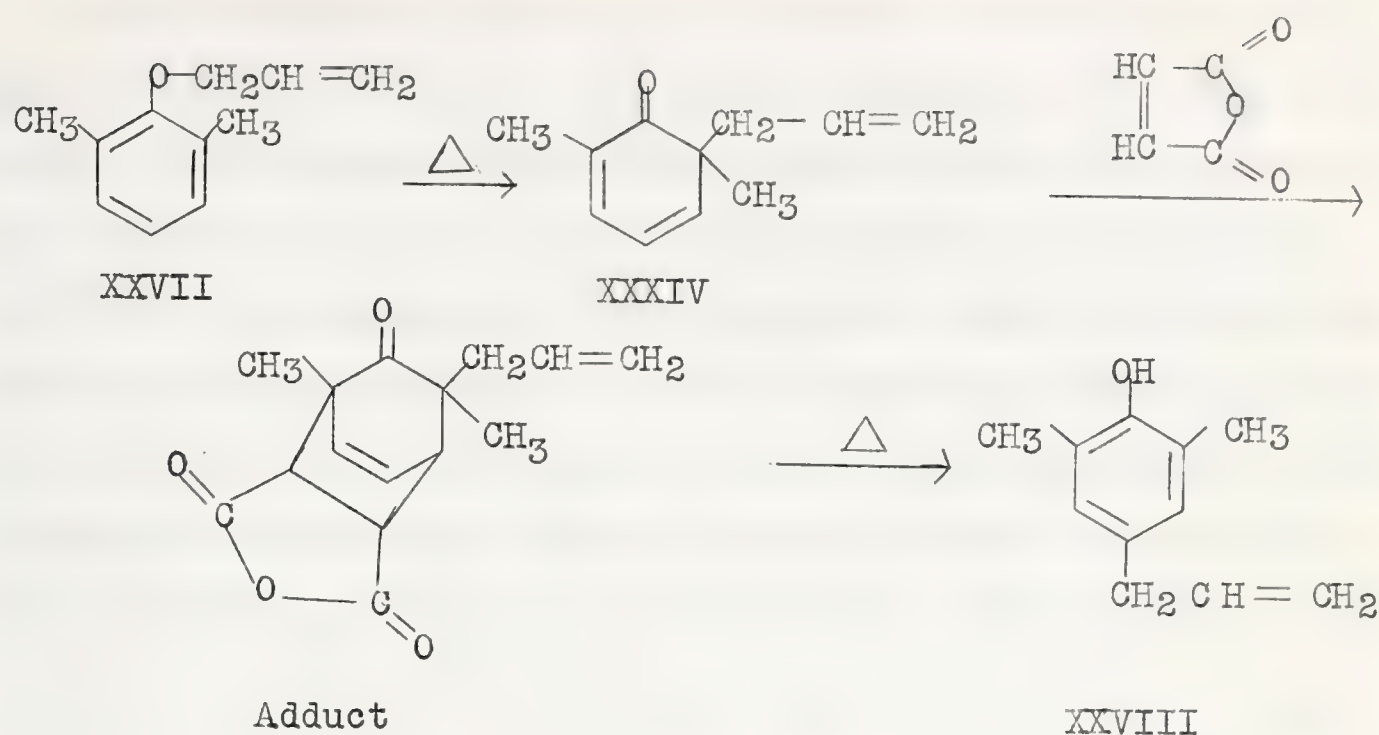
The observations discussed above support the proposal originally made by Hurd and Pollack (4) that the rearrangement of substituted allyl aryl ethers to the para position occurs by two consecutive steps - a shift of the allyl group with inversion to the ortho position as described previously for the ortho rearrangement, followed by another shift with inversion to the para position. The two inversions would then result in the observed overall non-inversion of the allyl moiety.

This proposed mechanism can be conveniently illustrated by the rearrangement of allyl 2,6-dimethylphenyl ether (XXVII) to 4-allyl-2,6-dimethylphenol (XXVIII). Thus, the first step would involve conversion of the ether, through a cyclic transition state (XXXIII), to 6-allyl-2,6-dimethyl-2,4-cyclohexadienone (XXXIV)

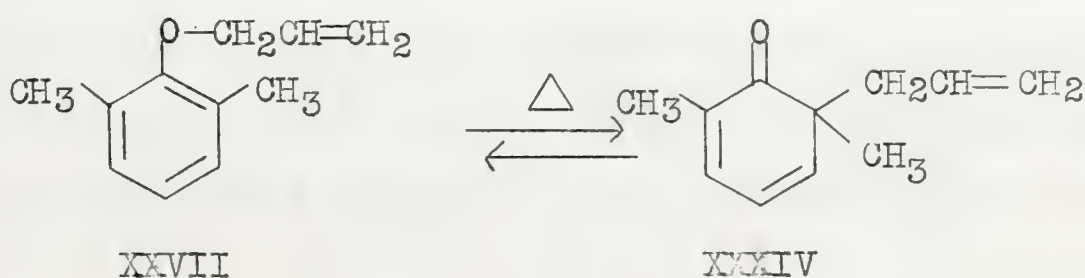
which cannot acquire stability by enolization, and therefore undergoes further allylic rearrangement via the transition state (XXXV) to form a second dienone (XXXVI) which, upon rapid aromatization, affords 4-allyl-2,6-dimethylphenol (XXVIII).



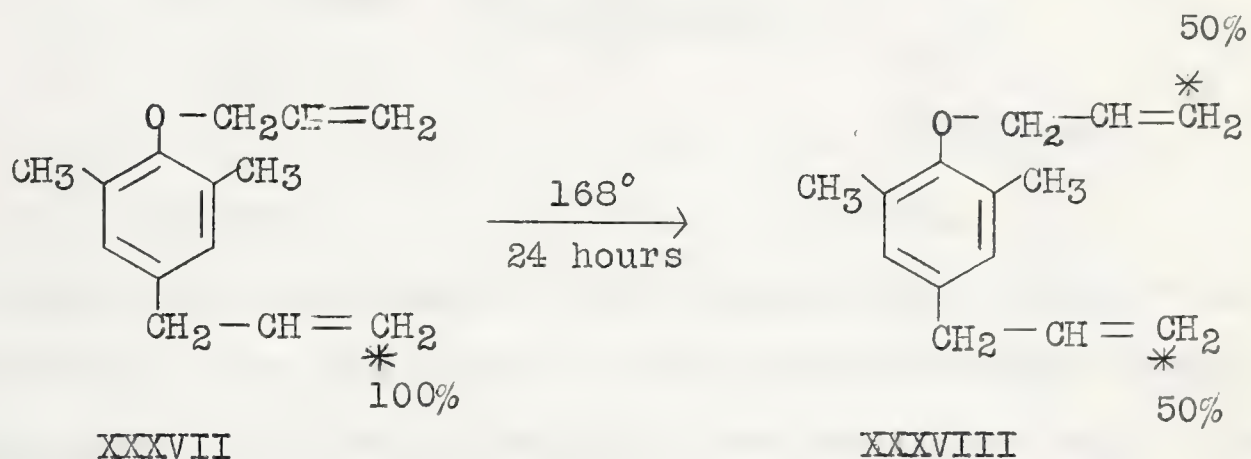
An imposing body of evidence has been gathered for the intervention of the dienone (XXXIV) as an intermediate in the para Claisen rearrangement (33-36). Possibly the most conclusive evidence was first reported by Conroy and Firestone (33), who found that allyl 2,6-dimethylphenyl ether (XXVII), when caused to rearrange in maleic anhydride, gave a small amount of Diels-Alder adduct, which, when heated, afforded the final rearranged product (XXVIII), as shown below. More recently, Kalberer and Schmid (36) reported a number of such reactions, in which several different dienone intermediates were trapped by means of a Diels-Alder reaction.



The preparation of the 6-allyl-2,6-dimethyl-2,4-cyclohexadienone (XXXIV) itself, by treatment of a suspension of the sodium salt of 2,6-dimethylphenol in benzene with allyl bromide, was accomplished by Curtin and Crawford (35) in 1957. These authors found that when the dienone was heated to a temperature above 70°, it rearranged to afford a mixture of allyl 2,6-dimethylphenyl ether and 4-allyl-2,6-dimethylphenol, in a ratio of 1:2.7. These results not only lend support to the proposed intervention of the dienone as an intermediate in the para Claisen rearrangement, but also indicate the reversible nature of the first step of the reaction, involving conversion of the original ether (XXVII) to the dienone intermediate (XXXIV).



This reversible formation of dienone intermediates in the para Claisen rearrangement has been demonstrated by a number of workers (34, 37, 38). Thus, for example, Schmid and co-workers (37) studied the effect of prolonged heating on allyl 4-allyl (γ -C¹⁴)-2,6-dimethylphenyl ether (XXXVII). When this ether was heated for twenty-four hours in diethylaniline at 168°, and then recovered, it was found that the radioactivity had become equally distributed between the γ -carbon atoms of the O- and C-allyl groups (XXXVIII), thus clearly showing the reversibility of the



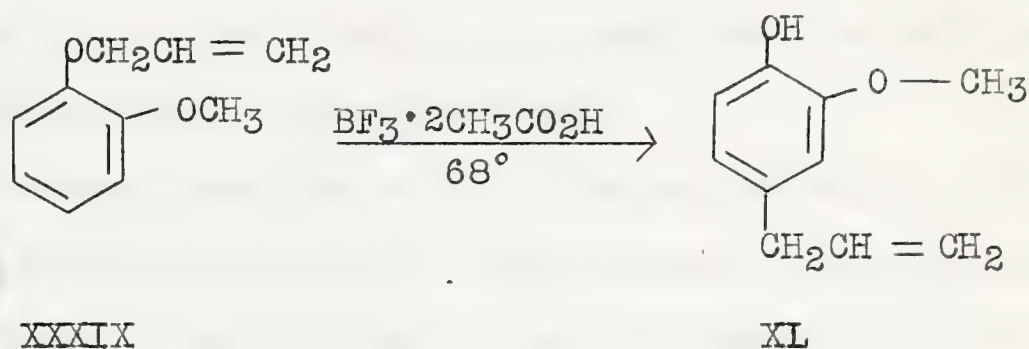
various steps of the reaction leading to para rearrangement.

C. The Acid-Catalyzed Claisen Rearrangement

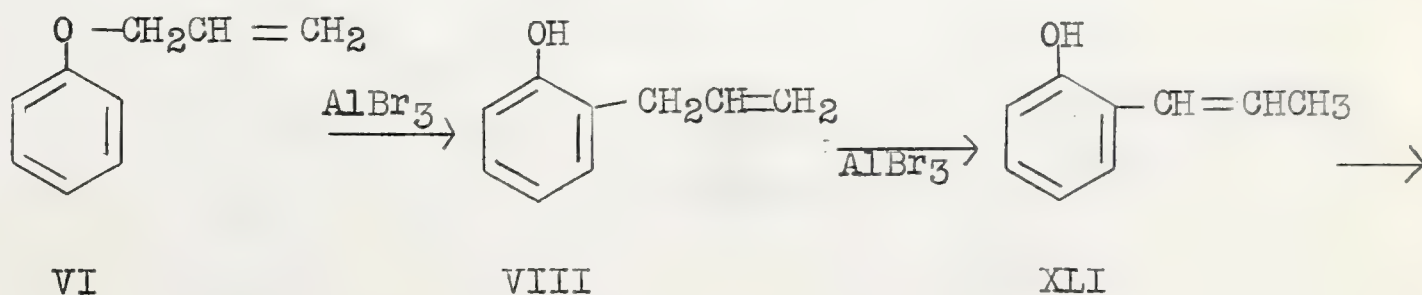
Although a great deal of work has been published concerning the thermal rearrangement of allyl aryl ethers, only a small number of investigations have been concerned with the effect of acidic reagents on this reaction. That the Claisen rearrangement might be catalyzed by acid was first shown by Tarbell and Kincaid. A kinetic study of the rearrangement of allyl 2,6-dimethylphenyl ether in diphenyl ether revealed that the addition of 1% and of 2.5% acetic acid increased the rate of the reaction 28% and 42%

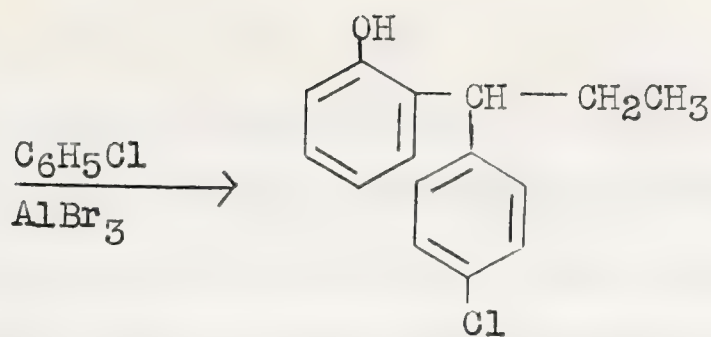
respectively (30).

Later observations disclosed that the rearrangement of allyl aryl ethers occurred at much lower temperatures, when Lewis acids were present, than those required for thermal reaction. For example, treatment of the allyl ether of guaiacol (XXXIX) with $\text{BF}_3 \cdot 2\text{CH}_3\text{CO}_2\text{H}$ at 68° gave 38% eugenol (XL) as well as smaller amounts of guaiacol, 6-allylguaiacol and the allyl ether of allylguaiacol or eugenol (39).



Petropoulos and Tarbell (40) reported that treatment of a solution of allyl phenyl ether (VI) in chlorobenzene at room temperature with aluminum bromide, resulted in the rapid formation of 1-(o-hydroxyphenyl)-1-(p-chlorophenyl)propane (XLII). This was explained by intramolecular rearrangement of the ether to o-allylphenol (VIII), followed by rapid isomerization of the latter to the propenyl compound (XLI), which then in turn reacted with the solvent in the presence of the Lewis acid to yield the propane derivative (XLII).

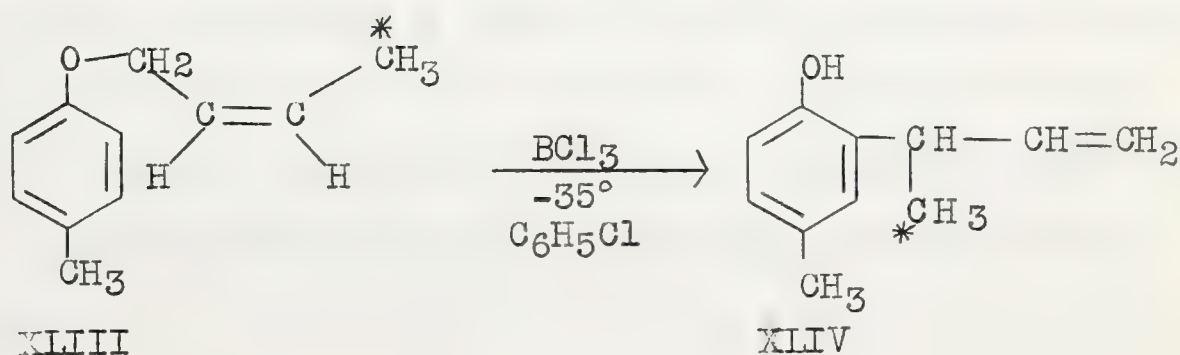




XLII

Boron trichloride also acts as a powerful catalyst in the Claisen rearrangement. Gerrard *et. al.* (41) reported that allyl phenyl ether, when treated with this Lewis acid at -80° , was converted exclusively to *o*-allylphenol.

A more recent study by Fahrni, Habich and Schmid (42) showed that boron trichloride effected facile rearrangement in high yields (90-98%) of allyl phenyl ether to *o*-allylphenol, allyl *p*-tolyl ether to 2-allyl-*p*-cresol, allyl 2,6-dimethylphenyl ether to a mixture of 3-allyl-2,6-dimethylphenol and 4-allyl-2,6-dimethylphenol, and also allyl mesityl ether to 3-allylmesitol. Furthermore, Schmid and co-workers (43) reported that treatment of a chlorobenzene solution of *cis*-4-(*p*-tolylloxy)-2-butene-(1- C^{14}) (XLIII) with boron trichloride at -35° , resulted in the exclusive formation of 3-(2-hydroxy-5-methylphenyl)-1-butene-(4- C^{14}) (XLIV). This result not only shows the powerful catalytic effect of boron trichloride on this reaction, but also indicates that the



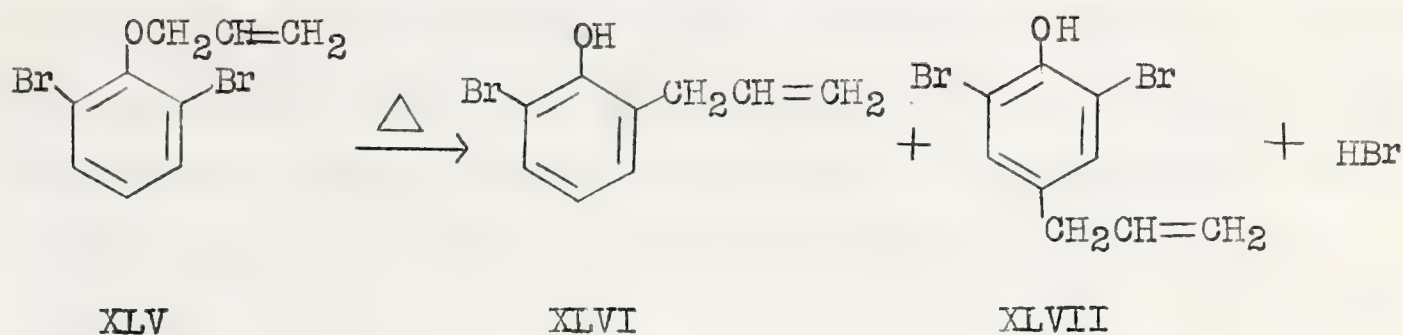
rearrangement, under these conditions, is strictly intramolecular.

In view of these previous results concerning the effect of acids on the Claisen rearrangement, it appeared likely that the Lewis acids zinc chloride and zinc bromide would also exert a catalytic effect on the rearrangement of allyl 2,6-dihalophenyl ethers.

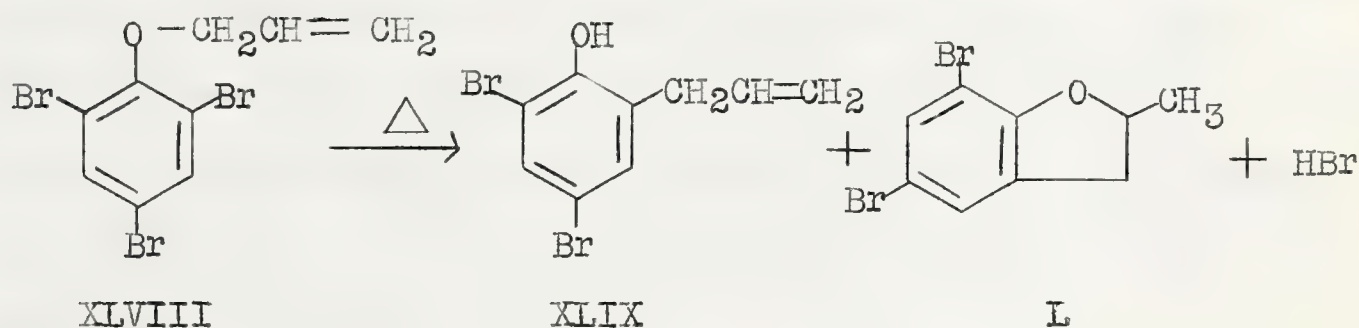
D. The Thermal Claisen Rearrangement of Allyl 2,6-Dihalophenyl Ethers

A number of reports have appeared in the literature concerning the effect of halogen substituents on the thermal Claisen rearrangement of allyl aryl ethers.

Hurd and Webb (44) found that ethers such as allyl o-bromophenyl ether, allyl 3,5-dibromophenyl ether, and allyl 2,4-dibromophenyl ether, which have at least one unsubstituted ortho position, rearrange normally to afford the corresponding o-allylphenols. However, these authors (45) also reported that rearrangement to the para position goes poorly in the case of ethers which contain bromine atoms in the two ortho positions. Thus, allyl 2,6-dibromophenyl ether (XLV) gave, upon pyrolysis, what appeared to be a mixture of 2-allyl-6-bromophenol (XLVI) and 4-allyl-2,6-dibromophenol (XLVII), along with simultaneous evolution of hydrogen bromide. Since the authors reported that they could not achieve separation of the two phenols, no separate yields were given, although the overall yield of the phenolic product was 37%. In addition, a considerable amount of tarry material was formed.



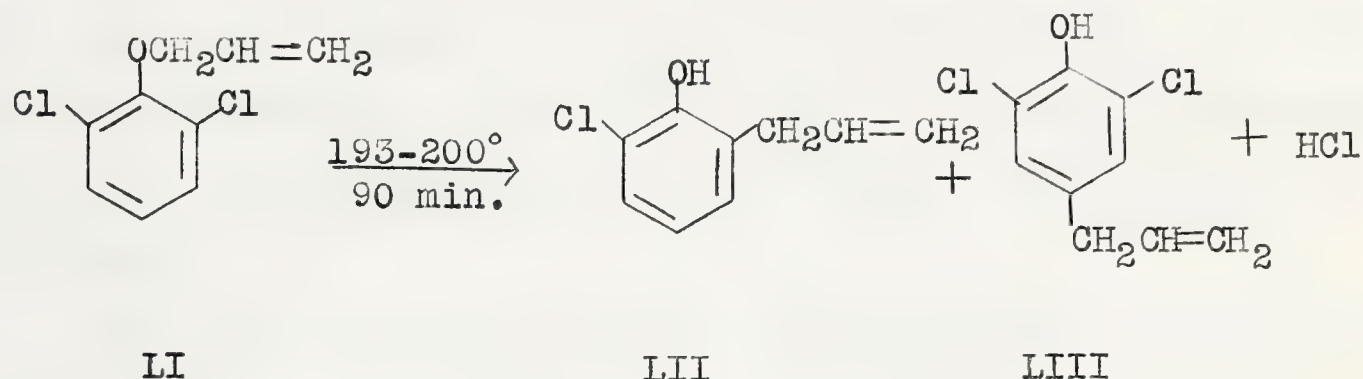
That the ortho bromine atom may be replaced by the incoming allyl group was further established (45) by the rearrangement of allyl 2,4,6-tribromophenyl ether (XLVIII), since 2-allyl-4,6-dibromophenol (XLIX) and 5,7-dibromo-2-methylcoumaran (L) were the reaction products. In addition, hydrogen bromide was again evolved.



Although coumarans are not usually formed in a strictly thermal Claisen rearrangement, the formation of the 5,7-dibromo-2-methylcoumaran (L) in the reaction described above is not surprising, since hydrogen bromide is also produced in the reaction mixture. Acidic reagents such as hydrobromic acid are known to cyclize o-allylphenols to the corresponding 2-methylcoumarans (14, 45).

The thermal rearrangement of allyl 2,6-dichlorophenyl ether (LI) afforded similar results to those obtained from the Claisen rearrangement of the corresponding dibromo compound. Tarbell and

Wilson (46) reported that when the pure ether (LI) was heated at 193-200° for ninety minutes, there was formed a mixture of 2-allyl-6-chlorophenol (LII) and 4-allyl-2,6-dichlorophenol (LIII), with simultaneous hydrogen chloride evolution. The reported yields of the phenols were 10% and 57% respectively.



Thus the main features of the thermal Claisen rearrangement of allyl 2,6-dihalophenyl ethers appeared to be (a) ortho rearrangement with simultaneous halogen elimination; (b) hydrogen halide evolution apparently accompanying step (a); (c) para rearrangement of the allyl group, with retention of the two ortho halogen atoms.

RESULTS AND DISCUSSION

For the sake of clarity and convenience, this section of the thesis is appropriately divided into a number of parts, each dealing with a somewhat distinct phase of our work.

The first part is concerned with a study of the zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether, and with a comparison of the results obtained from this investigation with those derived from the strictly thermal rearrangement of the ether.

The second section deals with the thermal rearrangement of allyl 2,6-dichlorophenyl ether in various solvents.

The results obtained from the rearrangement of allyl 2,6-dichlorophenyl ether in the presence of stannous chloride are presented in the third portion of this discussion.

The fourth segment is involved with the presentation of possible mechanisms which could be involved in the halogen migration which occurs during the zinc halide-catalyzed rearrangement of allyl 2,6-dihalophenyl ethers.

Finally, in the fifth and last part, the results obtained from the zinc bromide-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether and those from the zinc chloride-catalyzed rearrangement of allyl 2,6-dibromophenyl ether, are presented. These results, as well as those given in the previous sections, are discussed in terms of the mechanisms proposed for halogen migration.

1. The Zinc Chloride-Catalyzed Rearrangement of Allyl 2,6-Dichlorophenyl Ether

The first problem undertaken in our work was to determine the effect of zinc chloride on the Claisen rearrangement of allyl 2,6-dichlorophenyl ether. In view of previous observations concerning the Lewis acid-catalyzed rearrangement of allyl aryl ethers (39-43), it was felt that the Lewis acid, zinc chloride, should catalyze the rearrangement of allyl 2,6-dichlorophenyl ether, as well as bring about the migration of one of the chlorine atoms from the ortho to the para position, analogous to the findings of Carlin and Fisher (1) concerning the Fischer indole synthesis with 2,6-dichlorophenylhydrazones.

The choice of a suitable solvent for our reactions was of importance, since, in order to ensure sufficient solubility of the Lewis acids employed, the solvent would have to be of a polar nature or possess the ability for close association with the Lewis acid (e.g. benzene). Furthermore, a high boiling point was desirable in order that the reactions could be conveniently carried out over a wide temperature range. Nitrobenzene appeared to have these required properties, since it has been used extensively as a solvent for Lewis acids in the Friedel and Crafts reaction (47), and also has a relatively high boiling point (210°). This solvent proved to be satisfactory and was employed throughout our work concerning the zinc halide-catalyzed rearrangement of allyl 2,6-dihalophenyl ethers.

The results obtained from the zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether in nitrobenzene

TABLE I
The Zinc Chloride-Catalyzed Rearrangement of Allyl 2,6-Dichlorophenyl Ether
in Nitrobenzene Solution
(Concentration of ether: 0.15 mole of ether in 1 mole of nitrobenzene.
Molar ratio of zinc chloride to ether = 2:1^a)

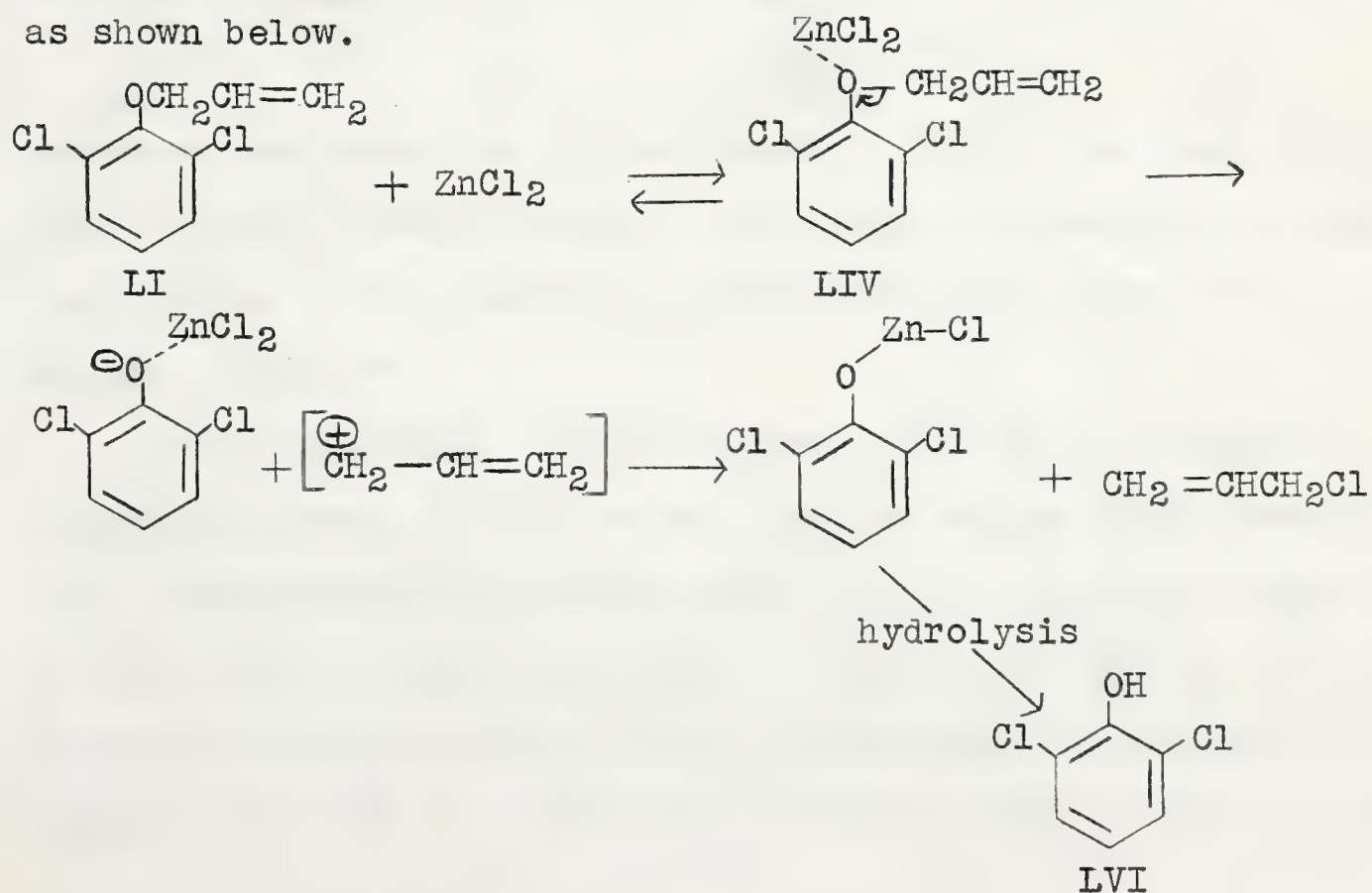
Expt. No.	Reaction Time and Temperature	Composition of Reaction Mixture ^b (%)		
		Allyl 2,6-dichlorophenyl ether	2,6-Dichlorophenol	2-Allyl-4,6-dichlorophenol
1.	130-135° 28 hr.	13	4	83
				Trace
2.	140-145° 24 hr.	Trace	4	91
				5
3.	150-155° 20 hr.	Nil	4	88
				8
4.	180-185° 1 hr.	Nil	16	77
				7
	5 hr.	Nil	16	30
				54

- a. Not all of the zinc chloride dissolved.
- b. In separate tests, the products were found to be stable under the reaction conditions, except that the 2-allyl-4,6-dichlorophenol was slowly converted to the 5,7-dichloro-2-methylcoumaran only.
- c. This was a single reaction from which, after 1 hour, a sample was taken for analysis giving the results shown. After 5 hours a second sample was removed from the reaction mixture and analyzed.

(ii) Ether Cleavage

A certain amount of ether cleavage occurred during the reaction of allyl 2,6-dichlorophenyl ether with zinc chloride. At lower temperatures (140-160°) approximately 4% of the total phenolic product was the cleavage material, 2,6-dichlorophenol, while at higher reaction temperatures (180°) the amount of cleavage product increased to 16% (Expt. Nos. 1-4, Table I, page 67).

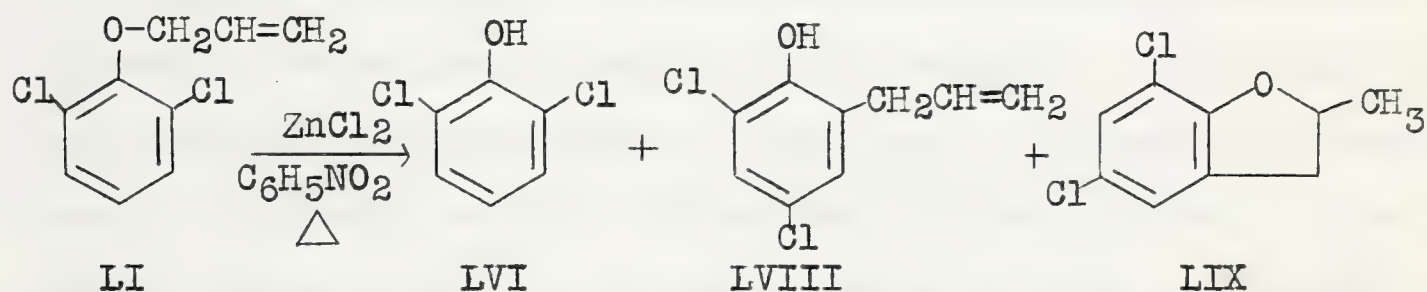
The formation of 2,6-dichlorophenol in this reaction is not surprising, since it is a well known fact that ethers cleave when treated with Lewis acids (48). For example, Hughes and Thompson (49) reported that the treatment of anisole with aluminum chloride at 100° for two hours gave a quantitative yield of phenol and methyl chloride. Thus, the occurrence of 2,6-dichlorophenol (LVI) in our reactions can readily be explained by the association of the zinc chloride with the allyl 2,6-dichlorophenyl ether (LI) to give the complex (LIV), which then cleaves in the usual manner, as shown below.



The exact fate of the allyl group in this cleavage reaction was not investigated, but it is very likely that allyl chloride was produced, analogous to other Lewis acid-promoted ether cleavages (48).

(iii) Chlorine Migration

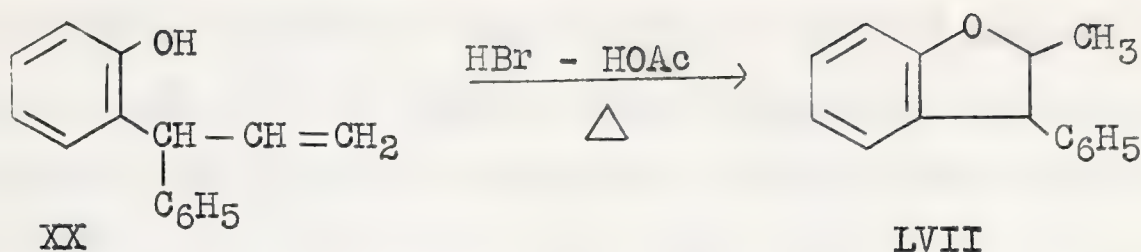
As in the case of the Fischer cyclization of 2,6-dichlorophenylhydrazones (1), chlorine migration also occurred during the zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether (LI) in nitrobenzene at 140-160°, since the products, in addition to the relatively small amount of ether cleavage product (LVI), were 2-allyl-4,6-dichlorophenol (LVIII) (88-91%) and 5,7-dichloro-2-methylcoumaran (LIX) (4-8%). Higher reaction temperatures



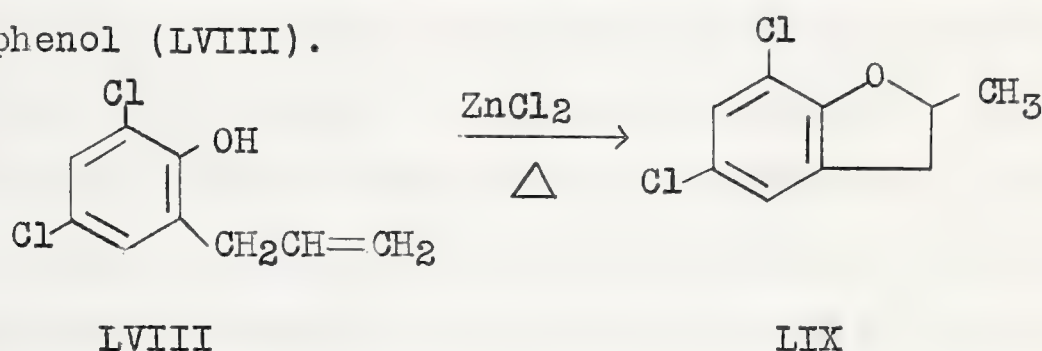
enhanced the formation of the coumaran (Expt. Nos. 1-3, Table I, page 67) and it was shown that the yield of coumaran increased at the expense of the 2-allyl-4,6-dichlorophenol (Expt. No. 4, Table I, page 67).

The cyclization of o-allylphenols to the corresponding 2-methylcoumarans by acid catalysts such as pyridine hydrochloride (50), hydrobromic acid-acetic acid (14, 45), or formic acid (51) is well known. Thus, for example, Claisen and Tietze (14) prepared 2-methyl-3-phenylcoumaran (LVII) in 86% yield by heating 2-(α -phenylallyl)phenol (XX) in a boiling mixture of acetic acid and hydro-

bromic acid for one hour.



The formation of 5,7-dichloro-2-methylcoumaran (LIX) in our reactions is therefore readily understood, and must have resulted from the zinc chloride-catalyzed ring closure of 2-allyl-4,6-dichlorophenol (LVIII).



Product analysis in the work described above was carried out by means of vapor phase chromatography (v.p.c.). The products were identified by comparison of their v.p.c. retention times with those of authentic samples, as well as by their isolation from the reaction mixtures and comparison of their infrared and nuclear magnetic resonance spectra with those of the authentic compounds. Thus, for example, careful fractionation of the reaction mixture from experiment number 4, Table I, page 67, permitted the isolation of all three products indicated. The coumaran was found to be identical in all respects with the compound obtained by ring closure of 2-allyl-4,6-dichlorophenol according to Claisen's general method (14, 45). Thus, when the dichlorophenol was heated in a boiling mixture of hydrobromic acid and acetic acid, 5,7-dichloro-2-methylcoumaran was formed in 48% yield. The same reaction occurred when the dichlorophenol was heated with zinc chloride in nitrobenzene (Table I, footnote b, page 67).

Attempted extraction of the phenolic products from ethereal solutions of the reaction mixtures with Claisen's alkali (52), a procedure employed in a recent report concerning the Claisen rearrangement (21) (although generally Claisen alkali extractions are made from hydrocarbon solvents (53)) still left a considerable portion of the 2-allyl-4,6-dichlorophenol in the neutral fractions. In fact, synthetic mixtures of 2-allyl-4,6-dichlorophenol, diethyl ether and diphenyl ether, extracted three times with Claisen's alkali, also gave incomplete separation of the phenol, although phenol extraction from this medium was somewhat better than that from the nitrobenzene-ether solvent. Accordingly, to avoid such loss of phenol, alkaline treatment was omitted and v. p. c. analyses were performed, quite satisfactorily, directly on samples of the total reaction mixtures. This procedure was employed throughout our work.

Thermal Rearrangement of Allyl 2,6-Dichlorophenyl Ether

In order to achieve a direct comparison of the results obtained from the zinc chloride-catalyzed rearrangement with those derived from the thermal rearrangement of allyl 2,6-dichlorophenyl ether, the thermal reaction of this ether was examined.

The results of this investigation, which are tabulated in Table II, page 72, clearly show that the thermal rearrangement of allyl 2,6-dichlorophenyl ether afforded a mixture of reaction products much different from that obtained from the rearrangement of the ether in the presence of zinc chloride.

As noted in the introduction to this work, Tarbell and Wilson

n

TABLE II

The Thermal Rearrangement of Allyl 2,6-Dichlorophenyl Ether

(Concentration of ether: 0.15 mole of ether in 1 mole of nitrobenzene.
In Expt. Nos. 3 and 5, molar ratio of lithium chloride to ether = 2:1^a)

Expt. No.	Reaction Conditions	Composition of Reaction Mixture ^b (%)			
		Allyl 2,6-dichlorophenyl ether	2-Allyl-6-chlorophenol	2-Allyl-4,6-dichlorophenol	4-Allyl-2,6-dichlorophenol
1.	No solvent 193-200° 90 min.	Nil	7	2	91
2.	In nitrobenzene 180-185° 3 hr. 10 hr.	Nil Nil	11 11	8 8	81 81
3.	In nitrobenzene + LiCl 180-185° 3 hr.	Nil	15	11	74
4.	In nitrobenzene 140-145° 24 hr.	40	8	3	49
5.	In nitrobenzene + LiCl 140-145° 24 hr.	42	15	4	39

a. Not all of the lithium chloride dissolved.

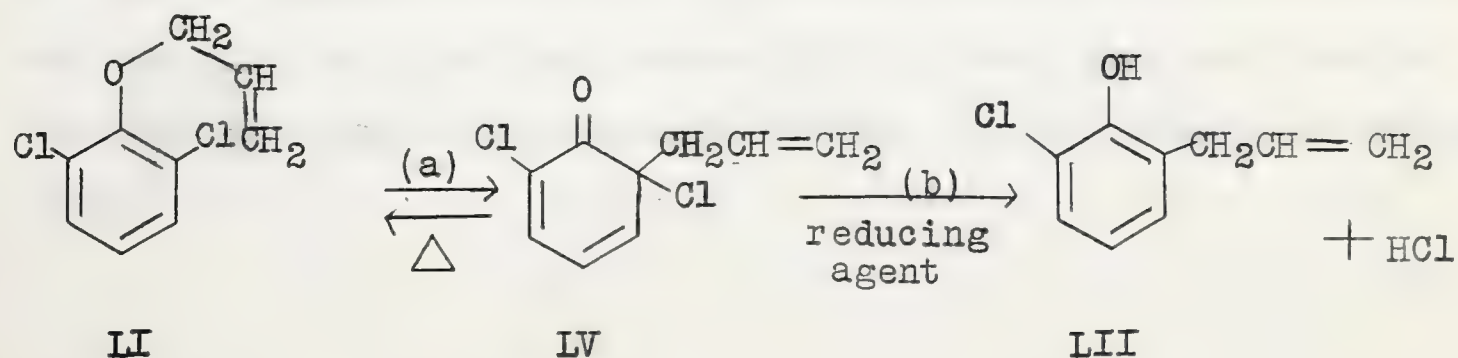
b. All of the phenolic products were found to be stable under the reaction conditions (shown by separate tests).

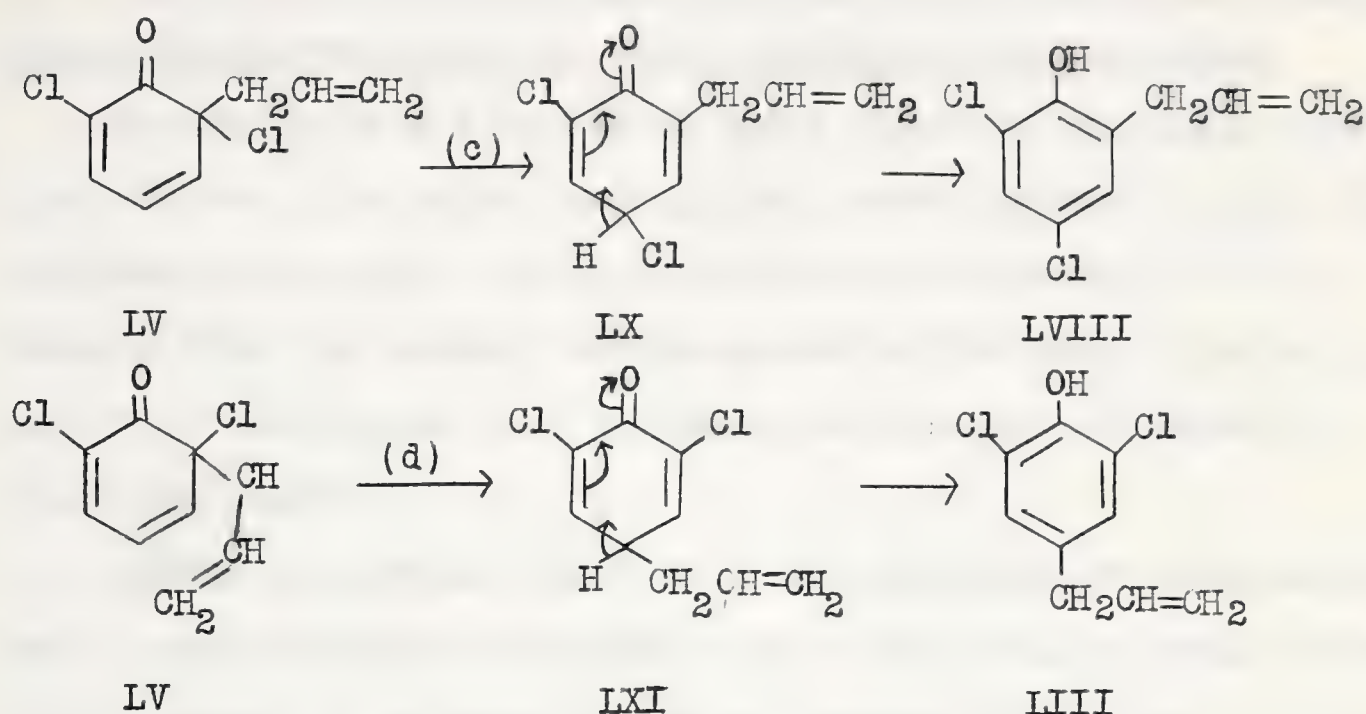
(46) reported that pyrolysis of pure allyl 2,6-dichlorophenyl ether at 193-200° for ninety minutes resulted in the formation of a mixture of 2-allyl-6-chlorophenol and 4-allyl-2,6-dichlorophenol, with the latter predominating very largely. Our repetition of this experiment disclosed that there was formed, in addition to these two compounds, a small amount (2%) of 2-allyl-4,6-dichlorophenol, obviously produced by chlorine migration from the ortho to the para position (Expt. No. 1, Table II, page 72).

When nitrobenzene was employed as solvent in the thermal rearrangement of allyl 2,6-dichlorophenyl ether, the amount of 2-allyl-4,6-dichlorophenol increased to 8%. The yield of 2-allyl-6-chlorophenol was also increased (Expt. No. 2, Table II, page 72). The addition of lithium chloride to the nitrobenzene solution further enhanced both the amount of halogen migration product (11%) and halogen elimination product (Expt. No. 3, Table II, page 72), although no catalysis of the disappearance of the original ether appeared to occur (Expt. Nos. 4 and 5, Table II, page 72).

These results indicate that halogen migration can occur to some extent even when zinc chloride is not present, and is assisted in the purely thermal rearrangement by a polar reaction medium.

The formation of the products in the thermal rearrangement of allyl 2,6-dichlorophenyl ether can be explained by the following reaction scheme.



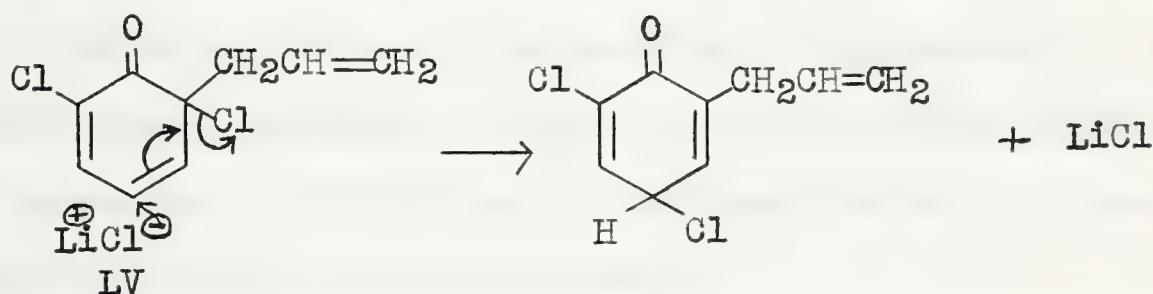


The first step was the thermal transformation of the ether (LI), via route a, to the dienone (LV), which then, in turn, underwent three competitive reactions. The first (route b), which must have involved oxidation of some component of the reaction mixture, such as reactant, products, or solvent, resulted in the reductive elimination of the allylic chlorine to form the reduction product 2-allyl-6-chlorophenol (LII). The second was the allylic migration of the chlorine from the ortho to the para position (route c), resulting in the formation of the dienone (LX), which aromatized rapidly to the chlorine migration product, 2-allyl-4,6-dichlorophenol (LVIII). The final transformation of the dienone (LV) was that of para rearrangement of the allyl group, via route d, to give the dienone (LXI), which, upon enolization, afforded the para rearrangement product, 4-allyl-2,6-dichlorophenol (LIII).

Comparison of the Thermal Rearrangement with the Zinc Chloride-Catalyzed Rearrangement of Allyl 2,6-Dichlorophenyl Ether

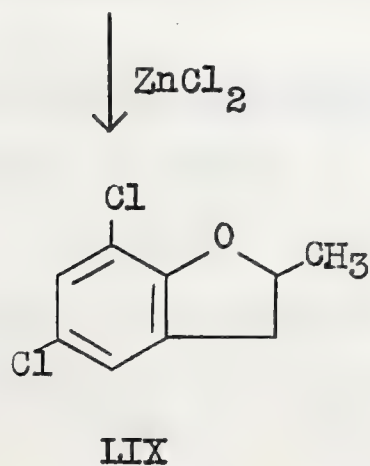
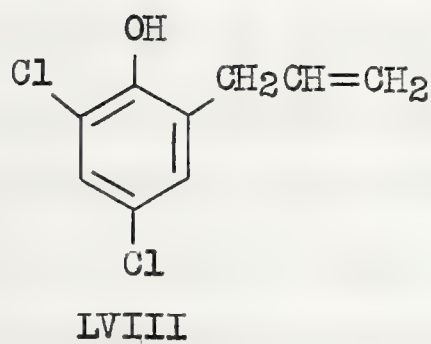
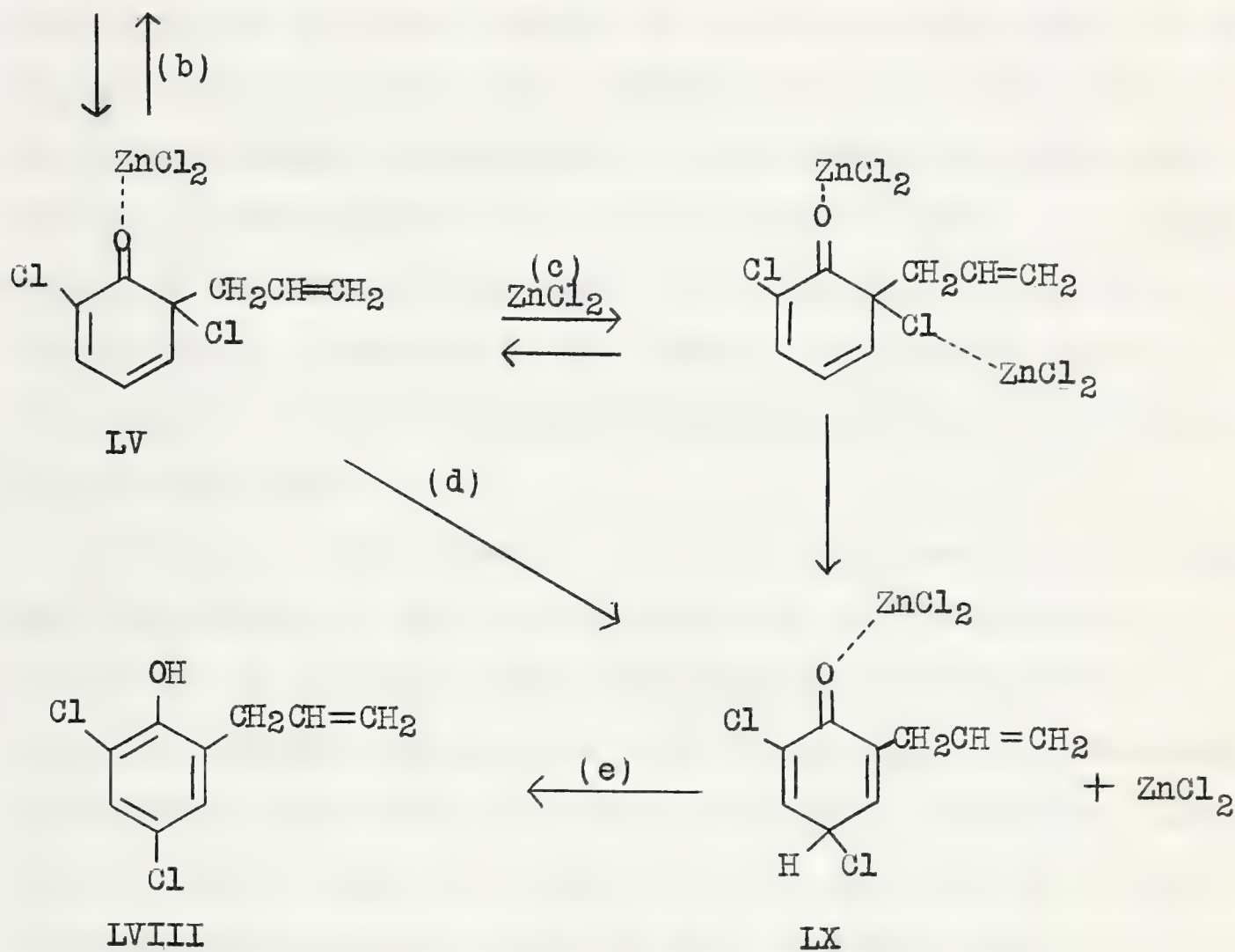
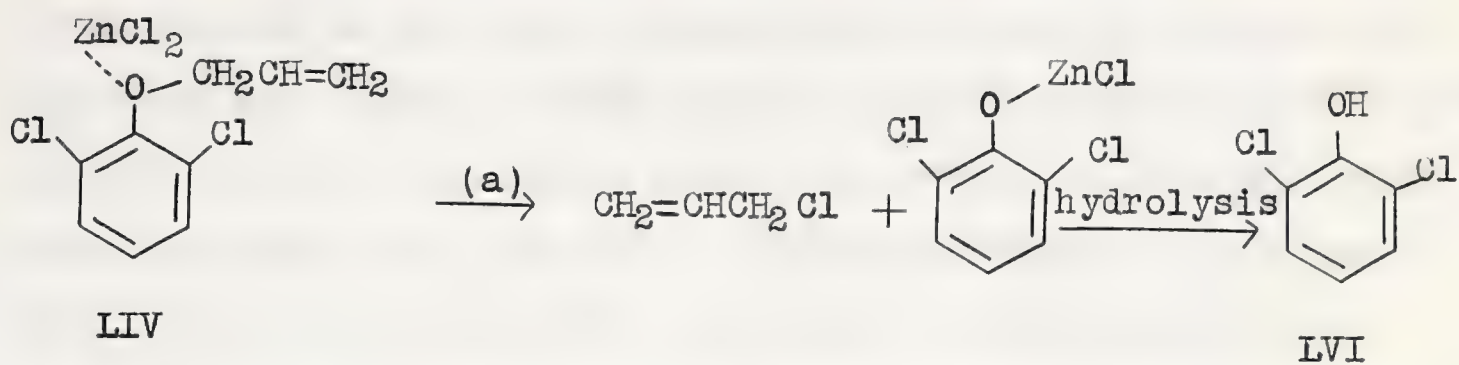
A clue as to the manner in which chlorine migration takes place in the zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether can be obtained by a comparison of the results from the thermal rearrangement of the ether (Table II, page 72), with those from the Lewis acid-catalyzed reaction (Table I, page 67).

Since the thermal reaction in the presence of lithium chloride gave, under otherwise identical conditions, only a small increase in the amount of halogen migration product (11%, Expt. No. 3, Table II, page 72) over that obtained without the chloride (8%, Expt. No. 2, Table II, page 72), it appears that there was little or no participation of the lithium chloride in the formation of the chlorine migration product via reaction with the dienone (LV) as indicated below. Indeed, the small increase in the



amount of halogen migration could have been caused entirely by an increase in the polarity of the reaction medium.

Let us now consider the zinc chloride-catalyzed rearrangement. In view of the fact that the addition of zinc chloride to the reaction mixture resulted nearly exclusively in the formation of chlorine migration product (96%, Expt. No. 2, Table I, page 67) while the addition of lithium chloride made very little difference



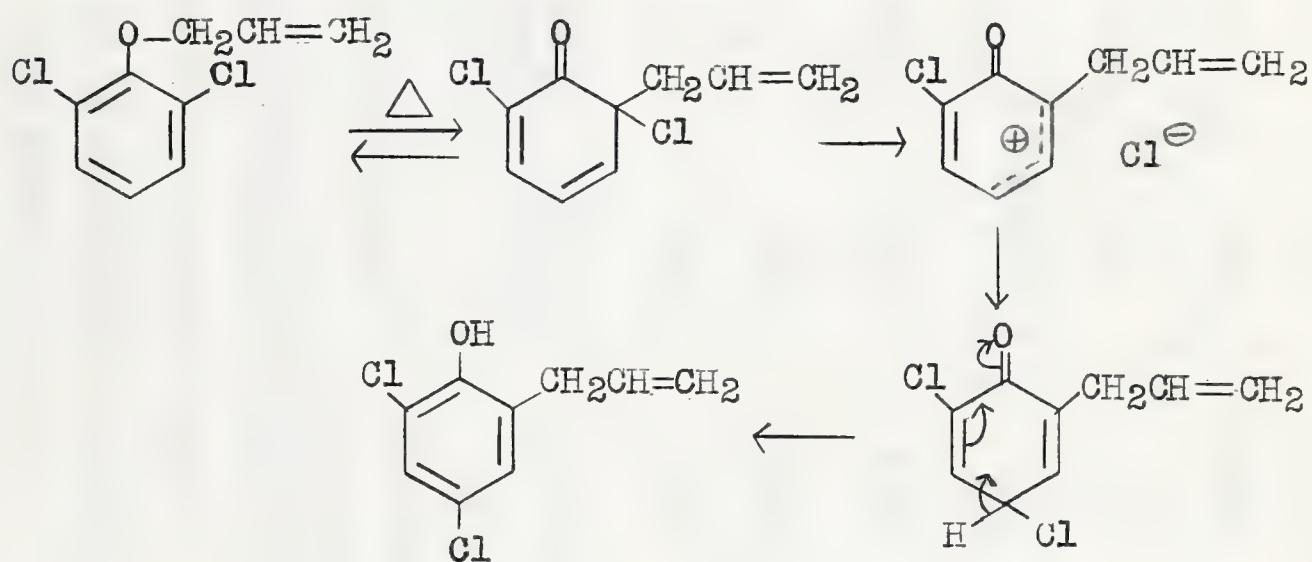
The zinc chloride-allyl 2,6-dichlorophenyl ether complex (LIV) cleaved in the usual manner (48) via route a to form 2,6-dichlorophenol (LVI). Simultaneously there occurred a preferential intramolecular rearrangement of LIV by route b to form the intermediate dienone (LV), which then underwent chlorine migration to afford a second dienone (LX). Although this migration could have occurred to a small extent by a simple allylic shift of the halogen (route d) since this transformation also took place in the purely thermal rearrangement, it probably occurred chiefly through a participation by the zinc chloride (route c). Aromatization of the dienone (LX) gave the 2-allyl-4,6-dichlorophenol (LVIII) which, depending on the reaction conditions, partly cyclized to 5,7-dichloro-2-methylcoumaran (LIX) in the presence of the Lewis acid.

Although it now appears quite clear that the zinc chloride does participate in the halogen migration in this reaction, nothing has as yet been said concerning the exact manner in which the halogen rearrangement takes place after the association of the Lewis acid with the allylic chlorine. A detailed discussion of the possible mechanisms which could be involved in the zinc halide-assisted halogen migration will be given later.

2. The Thermal Rearrangement of Allyl 2,6-Dichlorophenyl Ether in Various Solvents

As noted in the foregoing section of this discussion, the thermal rearrangement of pure allyl 2,6-dichlorophenyl ether gave, in addition to the previously reported products, 2-allyl-6-chloro-

phenol and 4-allyl-2,6-dichlorophenol (46), a small amount (2%) of 2-allyl-4,6-dichlorophenol, which obviously resulted from migration of chlorine from the ortho to the para position of the benzene nucleus. Furthermore, the amount of chlorine migration increased to 8% when the rearrangement was carried out in nitrobenzene solution, and was still further enhanced (11%) by application of nitrobenzene-lithium chloride as the reaction medium. These results indicated that the reaction leading to the halogen migration product was assisted by a polar reaction medium, and that the process was of an ionic nature, as shown below.



It was thought to be of interest, therefore, to investigate the effect of polarity of solvent on the extent of halogen migration in the thermal rearrangement of allyl 2,6-dichlorophenyl ether. Hence, the rearrangement of this ether was carried out in a number of solvents whose polarity, as indicated by their dielectric constants, differed widely. The number of solvents was, of course, necessarily limited to those of suitable physical

TABLE III

Solvent Effect on the Halogen Migration in the Thermal Rearrangement of

Allyl 2,6-Dichlorophenyl Ether

(Concentration of ether: 0.05 mole of ether in 50 ml. of solvent)

Expt. No.	Solvent and Reaction Conditions ^a	Dielectric Constant of Solvent ^b	Composition of Reaction Mixture ^c (%)				Character of the Reaction
			2,6- Dichloro- phenol	2-Allyl- 6-chloro- phenol	2-Allyl- 4,6- dichloro- phenol	4-Allyl- 2,6- dichloro- phenol	
1.	Decalin 180-185°, 8 hr.	2.2	Nil	64 ^d	6 ^d	30	Considerable decomposition
2.	Diphenyl ether 180-185°, 6 hr.	3.6	Nil	3	Nil	97	Very little decomposition
3.	o-Dichlorobenzene 178°, 9 hr.	7.5	Nil	Trace	Nil	~100	Clean, no decomposition
4.	No solvent 193-200°, 90 min.	?	Nil	7	2	91	Small amount of decomposition
5.	Phenol 175-180°, 2 hr.	9.9	10	9 ^e	11	63	Moderate amount of decomposition
6.	Benzonitrile 180-185°, 4.5 hr.	25.2	Nil	2	3	95	Very little decomposition
7.	N,N-Diethylformamide 177°, 4.5 hr.	?	8	23	38	31	Much decomposition
8.	Nitrobenzene 180-185°, 4 hr.	36	Nil	14	7	79	Moderate amount of decomposition

TABLE III - Continued

9.	Nitrobenzene + LiCl 180-185°, 3 hr.	?	Nil	15	11	74	Moderate amount of decomposition
10.	N-Methylformamide 180°, 2.7 hr.	190	6	59	25	10	Very much decomposition

a. In all cases the reaction time was extended until all of the original ether had disappeared.

b. The solvents were arranged in order of increasing dielectric constant (at 20°). Those whose dielectric constants were unknown to us were placed in the order expected, e.g. N,N-diethylformamide is expected to have a dielectric constant not too much different from that of N,N-dimethylformamide (37.6). Values of the dielectric constants were obtained from several sources:

1. A. A. Maryotte and E. R. Smith. Table of dielectric constants of pure liquids. Natl. Bur. Standards Circ. 514. 1951.
2. Landhold-Börnstein. Zahlenwerte und Funktionen. II Band, 6 Teil. Springer-Verlag, Berlin, Germany. 1959.
3. G. R. Leader and J. F. Gormley. J. Am. Chem. Soc. 73, 5731 (1951).

c. In the cases where decomposition was apparent, separate tests showed that under the reaction conditions all the products were quite stable.

d. Analysis of samples of the reaction mixture showed that 2-allyl-6-chlorophenol was formed very early in the reaction (~10% after 0.5 hour reaction time) and that only very little (~1%) of 2-allyl-4,6-dichlorophenol was formed before 50% of the original ether had reacted.

e. Experiment number 5 also gave 5% of a substance which was found to be 7-chloro-2-methylcoumaran, no doubt derived from the cyclization of some of the 2-allyl-6-chlorophenol in the presence of the acidic phenol solvent. No coumaran was found in any of the other cases.

TABLE IV

Variation of the Dielectric Constants of Various
Organic Liquids with Temperature ^a

Substance	Dielectric Constant	Temperature (°C)
Chloroform	4.8	20
	3.7	100
	3.3	140
	2.9	180
<u>o</u> -Chloronitrobenzene	38	50
	32	80
	27	110
	24	140
	22	163
<u>m</u> -Chloronitrobenzene	21	50
	18	80
	16	110
	14	140
	13	160
Chlorobenzene	5.7	20
	5.6	25
	4.2	130
Nitrobenzene	34.8	25
	24.9	90
	22.7	110
	20.8	130
Aniline	6.9	20
	5.9	70
	4.5	184
Benzonitrile	25	25
	24	40
	22	70

a. Values cited in this table were taken from A. A. Maryotte and E. R. Smith. Table of dielectric constants of pure liquids. Natl. Bur. Standards Circ. 514. 1951.

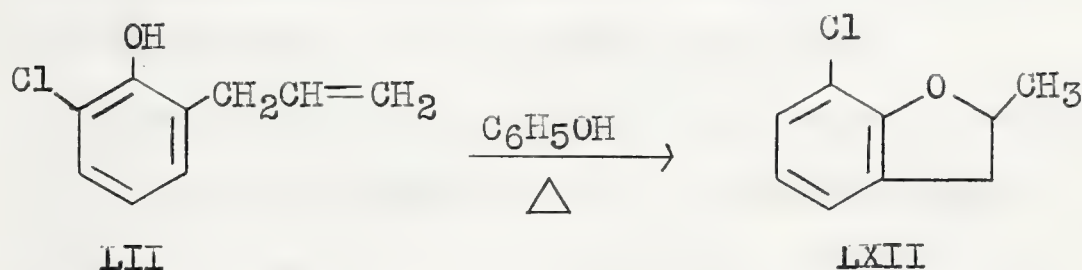
characteristics and chemical inertness, since, in order for the rearrangement to be carried out conveniently, the solvents had to possess a sufficiently high boiling point. The results obtained from this study are summarized in Table III, page 80.

Although the dielectric constants of the solvents employed have not been measured at the temperature of our reactions and although the decrease of dielectric constant with increasing temperature is somewhat different for different liquids, it is reasonable to assume that the relative dielectric constants, and hence the relative polarities, of a number of solvents would be roughly the same at 175-185° (the temperature of our reactions) as they are at 20-25° (the temperature at which dielectric constants are usually measured). Some support for this view is obtained by comparison of the dielectric constant values of several organic liquids at various temperatures (54, 55) (See Table IV, page 82).

The various products formed during the thermal rearrangement of allyl 2,6-dichlorophenyl ether in different solvents were 2,6-dichlorophenol, the result of cleavage of the original ether, 2-allyl-6-chlorophenol, resulting from ortho rearrangement of the allyl group with simultaneous reductive chlorine elimination, 2-allyl-4,6-dichlorophenol, stemming from ortho rearrangement of the allyl group along with an allylic chlorine migration from the ortho to the para position, and finally 4-allyl-2,6-dichlorophenol, produced by normal para rearrangement of the allyl moiety. For reasons of clarity, the formation of each of these products will be discussed separately.

(i) Formation of the Ether Cleavage Product, 2,6-Dichlorophenol

When allyl 2,6-dichlorophenyl ether was caused to rearrange in the solvent phenol at 175-180°, 10% of the total product of the reaction was the ether cleavage material 2,6-dichlorophenol (Expt. No. 5, Table III, page 80). The fact that the formation of this product is, as shown previously, characteristic of the zinc chloride catalyzed rearrangement of the ether, indicates that phenol not only catalyzes the Claisen rearrangement, as has been demonstrated by Goering and Jacobson (20), but also acts in a manner somewhat similar to that of a Lewis acid. Support for this conclusion is obtained from the observation that in our reaction there was also formed 5% of 7-chloro-2-methylcoumaran (LXII), obviously obtained by ring closure of 2-allyl-6-chlorophenol (LII), a purely acid-promoted reaction.



In both N,N-diethylformamide and N-methylformamide, the cleavage product also occurred (8% and 6% respectively, Expt. Nos. 7 and 10, Table III, page 81), but unaccompanied by coumaran formation. A great deal of decomposition took place in these two solvents during the rearrangement reaction, and the cause of the formation of the cleavage product is not known.

(ii) Formation of the Reduction Product, 2-Allyl-6-chlorophenol

The product resulting from ortho rearrangement of the allyl

group with simultaneous reductive chlorine elimination, 2-allyl-6-chlorophenol, was found in larger amounts when the rearrangement of allyl 2,6-dichlorophenyl ether was carried out in easily oxidizable solvents. Thus, in decalin, a non-polar solvent wherein considerable decomposition took place during the reaction, 64% of the product was 2-allyl-6-chlorophenol (Expt. No. 1, Table III, page 80). The fact that the reduction product appeared at a very early stage of the reaction, when relatively little phenolic product was present, and that it was present in such a large proportion at the end of the reaction, indicates that the solvent decalin did indeed participate as a reducing agent and that the monochlorophenol was not formed merely by oxidation of the phenolic products. However, due to the extensive decomposition, it was impossible to isolate oxidation products of decalin, such as tetralin, etc., to support this view.

When allyl 2,6-dichlorophenyl ether was caused to rearrange in N,N-diethylformamide and in N-methylformamide, much decomposition occurred in each case. The proportion of reduction product, 2-allyl-6-chlorophenol, was 23% and 59% respectively (Expt. Nos. 7 and 10, Table III, page 81), presumably also the result of facile oxidation of the solvent and/or its decomposition products.

When the rearrangement of allyl 2,6-dichlorophenyl ether was carried out in solvents which are themselves not readily oxidized, the amount of 2-allyl-6-chlorophenol formed decreased markedly compared with the extent of its formation in easily oxidizable solvents. In fact, in the solvents o-dichlorobenzene, benzonitrile, and diphenyl ether, none or only a very small amount (0-3%) of

the reduction product was found (Expt. Nos. 3, 6 and 2, respectively, Table III, page 80). It is likely that in these cases, as well as when no solvent was used, (Expt. No. 4, Table III) or when nitrobenzene was employed as solvent (Expt. Nos. 8 and 9, Table III, page 81), the phenolic products produced in the rearrangement could act as reducing agents under the reaction conditions to account for the formation of 2-allyl-6-chlorophenol.

(iii) Formation of the para Rearrangement Product, 4-Allyl-2,6-dichlorophenol

The product resulting from normal para rearrangement of allyl 2,6-dichlorophenyl ether, 4-allyl-2,6-dichlorophenol, was formed in varying amounts when the rearrangement of the ether was carried out in different solvents. It should be noted that the formation of this compound occurred best in solvents which are non-acidic, relatively non-polar, and which are not easily oxidized. Thus, for example, when the rearrangement was carried out in diphenyl ether solution or in o-dichlorobenzene solution, the yield of 4-allyl-2,6-dichlorophenol was nearly quantitative (97% and ~100% respectively, Expt. Nos. 2 and 3, Table III, page 80), while, at the other extreme, rearrangement of allyl 2,6-dichlorophenyl ether in decalin, which is easily oxidized, or in N-methylformamide, which is highly polar, as well as apparently easily oxidized, resulted in only 30% and 10% of the para rearrangement product, respectively (Expt. Nos. 1 and 10, Table III). Obviously, in the latter type of solvent, the reactions resulting in cleavage product, reduction product, and chlorine

migration product compete very favorably with that resulting in para rearrangement of the allyl group.

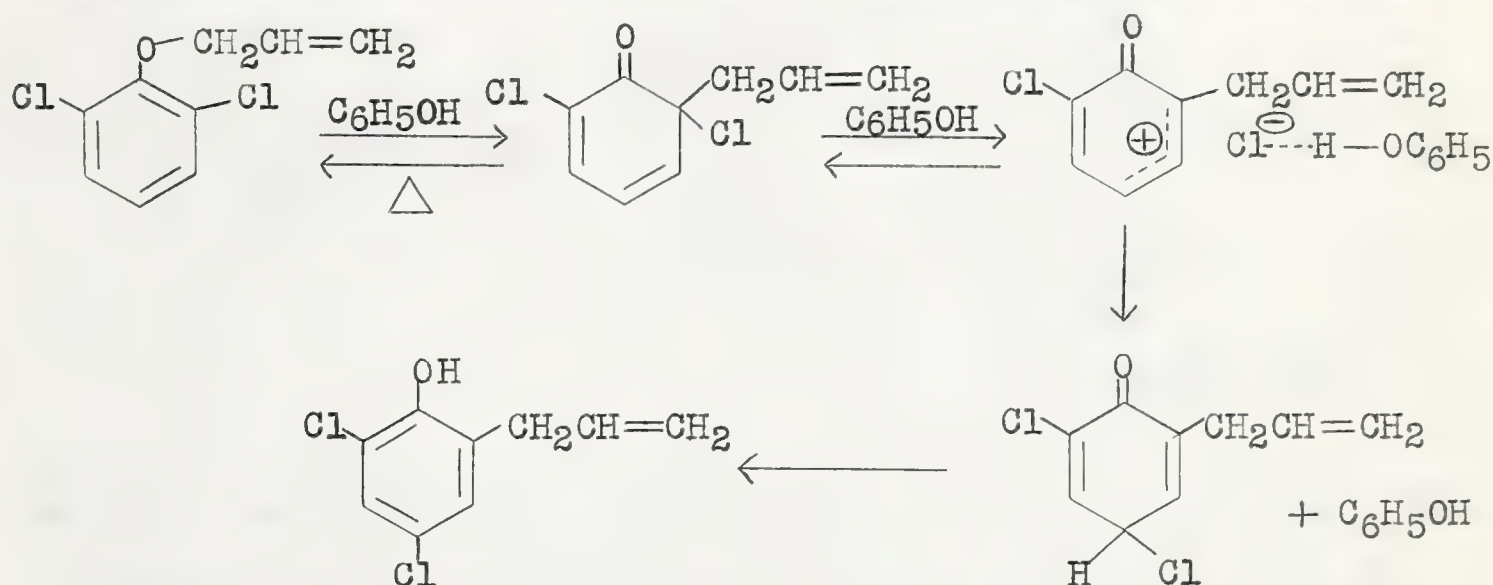
One of the interesting aspects of these results, and of possible synthetic importance, is the fact that rearrangement of allyl 2,6-dichlorophenyl ether in o-dichlorobenzene at 178°, affords a quantitative yield of 4-allyl-2,6-dichlorophenol. Thus, by proper choice of the reaction medium, one can eliminate the usual reactions competing with that of para rearrangement of the allyl substituent, hence resulting in a much superior method for the preparation of the 4-allyl-2,6-dichlorophenol.

(iv) Formation of the Chlorine Migration Product, 2-Allyl-4,6-dichlorophenol

Of primary interest in this study of the thermal rearrangement of allyl 2,6-dichlorophenyl ether in various solvents was the extent of formation of the halogen migration product, 2-allyl-4,6-dichlorophenol, and how it was affected by variation in the polarity of the reaction medium.

In non-acidic solvents of low polarity (diphenyl ether, o-dichlorobenzene, allyl 2,6-dichlorophenyl ether) little or no halogen migration occurred (0-2%, Expt. Nos. 2-4, Table III, page 80). The exception to this was decalin wherein 6% of the product was 2-allyl-4,6-dichlorophenol. However, since very little of this compound appeared before 50% of the original ether had reacted, it is likely that the phenolic products, associating minimally with the non-polar solvent decalin, and therefore to a greater extent with the remaining unreacted ether, aided the

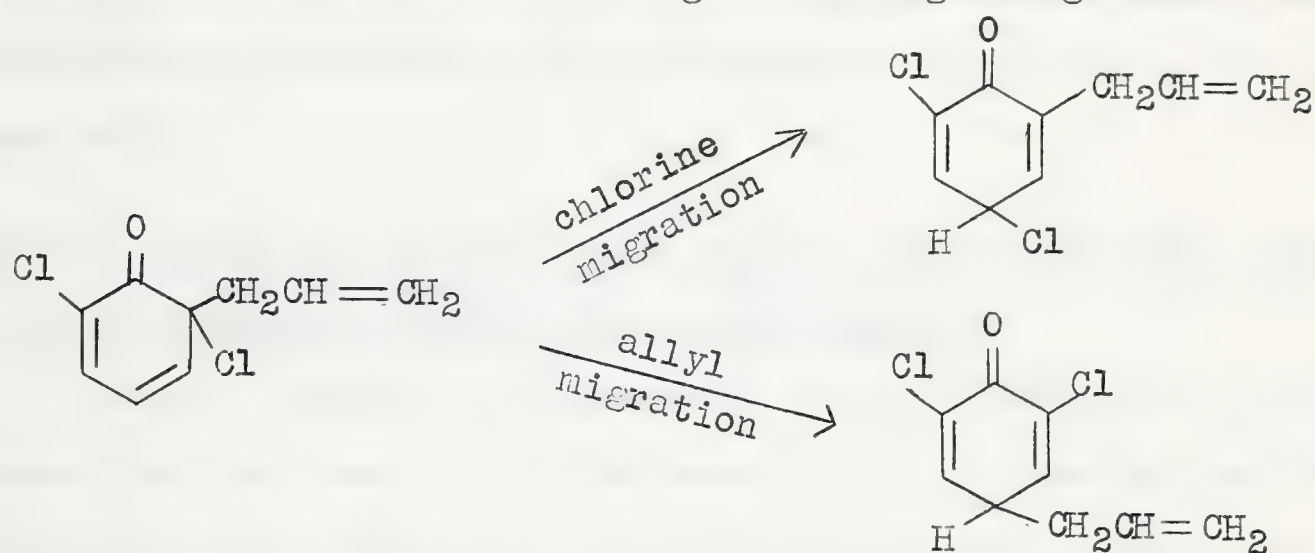
migration of halogen by protonation or hydrogen bonding by the acidic proton of the phenolic material with the allylic halogen in the intermediate dienone stage, thus promoting a greater degree of ionization of the allylic halogen. Similarly, the relatively large extent of chlorine migration which occurred during the rearrangement of allyl 2,6-dichlorophenyl ether in the relatively non-polar solvent phenol (11%, Expt. No. 5, Table III, page 80), was probably due to the same acid effect mentioned above brought about by association of the phenol solvent with the allylic chlorine of the dienone intermediate, as shown below.*



When the rearrangement of allyl 2,6-dichlorophenyl ether was carried out in the more highly polar but non-acidic solvents, those of dielectric constant greater than 30 (nitrobenzene, nitrobenzene + lithium chloride, N,N-diethylformamide, and N-methylformamide), there occurred a larger extent of chlorine migration (7-38%). However, the amount of halogen migration did not parallel the polarity of the solvent as expressed by dielectric constant (D.C.) values, since N-methylformamide (D.C. = 190)

*Hydrogen bonding with halogen is found in o-chlorophenol. See N. A. Puttnam, J. Chem. Soc. 5100 (1960).

yielded 25% of the product 2-allyl-4,6-dichlorophenol while N,N-diethylformamide (D.C.≈38) gave 38% of the halogen migration product (Expt. Nos. 10 and 7, respectively, Table III, page 81). This can be rationalized, however, if one considers that at the dienone stage there are two competing reactions, one in which the tertiary carbon's chlorine undergoes allylic rearrangement and the other in which the allyl group migrates to the para position, as indicated below. At this stage the halogen migration from C₂



to C₄ is assisted by the greater polarity of solvent while allyl migration from C₂ to C₄ is influenced only minimally if at all by increased solvent polarity (20). Thus, the ratio of chlorine migration to allyl migration should give an indication of the effect of polarity of solvent on the extent of halogen migration. In N-methylformamide the ratio is 25/10 while in N,N-diethylformamide it is 38/31. The larger ratio in N-methylformamide parallels its greater dielectric constant. The reductive removal of halogen, greater in the case of rearrangement in N-methylformamide than in N,N-diethylformamide, must also occur at the dienone stage and thus competes with halogen migration. It is

likely that if this reductive removal of halogen were not present, the difference in the ratio of halogen to allyl group migration in the solvents N-methylformamide and N,N-diethylformamide would be even greater.

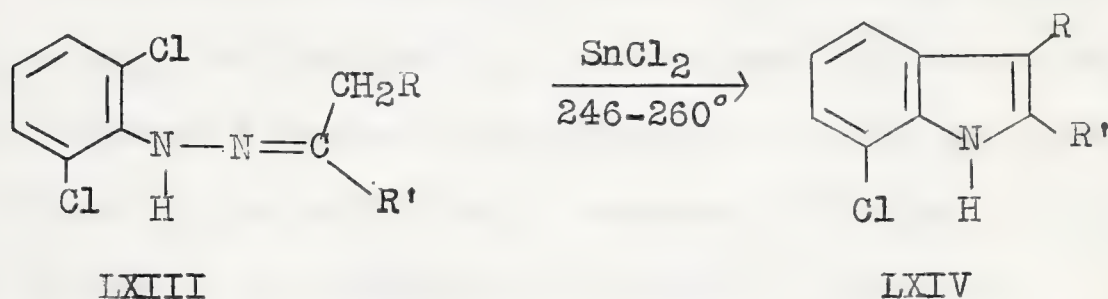
Benzonitrile (D.C.= 25.2) is considered to be a polar solvent, yet very little of either the halogen migration product, 2-allyl-4,6-dichlorophenol (3%), or the reduction product, 2-allyl-6-chlorophenol (2%) was formed when allyl 2,6-dichlorophenyl ether was caused to rearrange in this substance (Expt. No. 6, Table III, page 80).

Summary Concerning Factors which Affect Halogen Migration and Reductive Removal in the Thermal Rearrangement

From the results of experiments shown in Table III, page 80, concerning the thermal rearrangement of allyl 2,6-dichlorophenyl ether, it can be seen that a highly polar solvent (Expt. Nos. 7-10, Table III) does assist in the halogen migration as well as in the reductive elimination of one of the halogen atoms, with the latter depending upon the presence of an oxidizable substance. However, acidic solvents of lower polarity (and this includes phenolic products of the reaction to some extent) can accomplish the same thing. From the results obtained with benzonitrile as solvent, it appears that a moderate solvent polarity does not promote chlorine migration significantly, but requires some additional factor. There is thus no linear comparison between migration of halogen and polarity of solvent, due to the complicating effects of solvent and/or product acidity, as well as the effects of decomposition products.

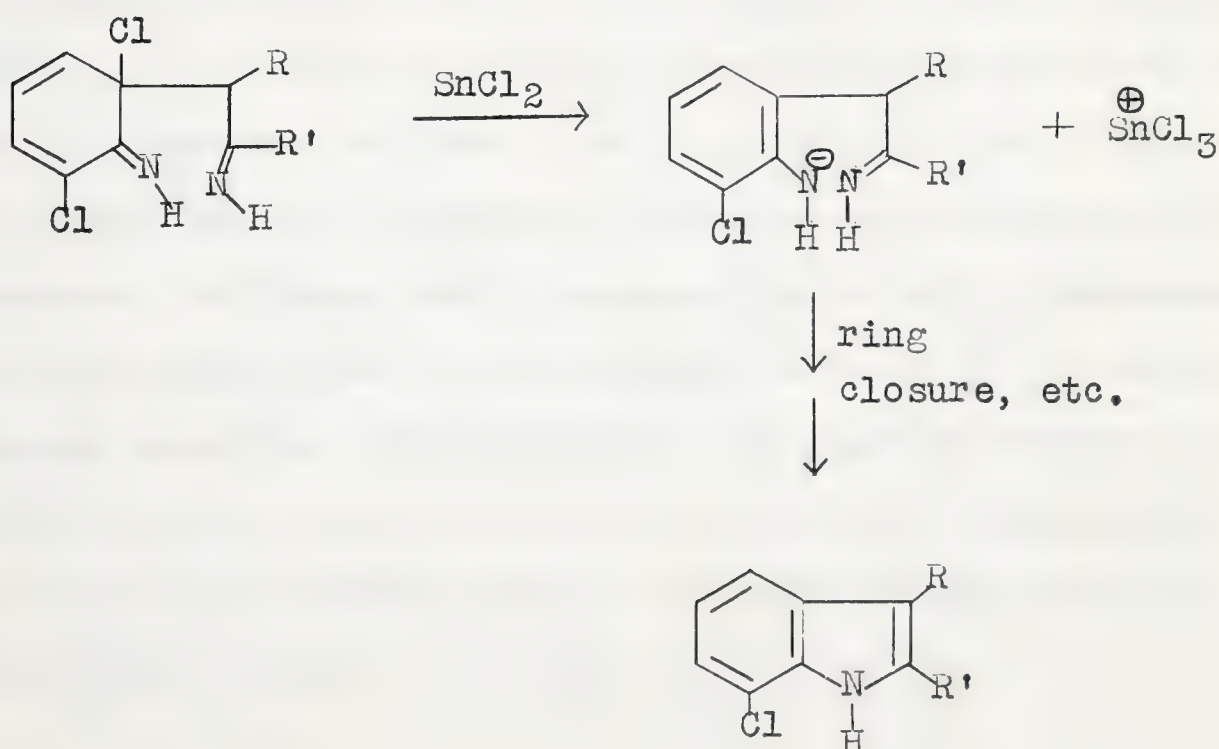
3. The Rearrangement of Allyl 2,6-Dichlorophenyl Ether in the Presence of Stannous Chloride

In 1952, Carlin, Wallace and Fisher (56) reported the conversion of several 2,6-dichlorophenylhydrazones (LXIII) to the corresponding 7-chloroindoles (LXIV) by fusion of the former with stannous chloride at 246-260°. The yields of product were generally



low (3-17%) and no 5,7-dichloroindoles, the result of halogen migration, were obtained from any of the reaction mixtures.

The formation of the 7-chloroindoles was explained by the reductive removal, by stannous chloride, of the allylic chlorine of the dienone imine intermediate, as shown below.



In view of the observation, as noted in the foregoing section, that the presence of oxidizable substances caused a competitive reductive elimination of one of the halogen atoms during the thermal rearrangement of allyl 2,6-dichlorophenyl ether, it was of interest to discover whether rearrangement of this ether in the presence of stannous chloride would yield only the monohalo product, 2-allyl-6-chlorophenol, analogous to the findings by Carlin et. al. (56) concerning the Fischer indole synthesis. The results obtained from the rearrangement of allyl 2,6-dichlorophenyl ether in the presence of stannous chloride in o-dichlorobenzene solution are summarized in Table V, page 93.

(i) Stannous Chloride as a Lewis Acid

Upon examination of the results presented in Table V, page 93, it is clearly seen that stannous chloride accelerated the rearrangement of allyl 2,6-dichlorophenyl ether since, for example, after eight hours reaction time 30% of the original ether was left when stannous chloride was present whereas, without stannous chloride, under otherwise identical conditions, 60% of the ether remained (compare sections A and B of Table V, page 93). Furthermore, both the ether cleavage product 2,6-dichlorophenol and the coumarans (7-chloro-2-methylcoumaran and 5,7-dichloro-2-methylcoumaran) were formed in the presence but not in the absence of stannous chloride. These products, as observed previously, are characteristic of the zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether, thus showing that stannous chloride also behaves as a Lewis acid.

TABLE V

Rearrangement of Allyl 2,6-Dichlorophenyl Ether in *o*-Dichlorobenzene

Reaction	Composition of Reaction Mixture ^a (%)						
Time (hr.)	Allyl 2,6-di-chlorophenyl ether	2,6-Di-chloro-phenol	2-Allyl-6-chloro-phenol	7-Chloro-2-methyl-coumaran	2-Allyl-4,6-dichloro-phenol	5,7-Dichloro-2-methyl-coumaran	4-Allyl-2,6-dichloro-phenol
A. With SnCl ₂ at 150-155° (Ratio of SnCl ₂ to ether = 1:1 ^b) (0.05 mole of SnCl ₂ and ether in 50 ml. of solvent)							
1	90	Nil	6	Nil	4	Nil	Nil
2	79	Trace	12	Nil	9	Nil	Nil
4	59	2	23	Nil	16	Nil	Nil
6	48	2	28	Nil	22	Nil	Nil
8	30	3	34	Nil	33	Nil	Nil
10	19	4	38	Nil	39	Nil	Nil
24	Nil	7	35	8	46	4	Nil
B. Without SnCl ₂ at 150-155° (0.05 mole of ether in 50 ml. of solvent)							
6	74	Nil	Nil	Nil	Nil	Nil	26
8	60	Nil	Nil	Nil	Nil	Nil	40
24	23	Nil	Nil	Nil	Nil	Nil	77
C. With SnCl ₂ at 150-155° (Ratio of SnCl ₂ to ether = 2:1 ^c) (0.012 mole of SnCl ₂ and 0.006 mole of ether in 125 ml. of solvent)							
24	Nil	Nil	37	Trace	63	Trace	Nil

a. Separate tests showed that all of the products were stable under the reaction conditions, except that in the presence of stannous chloride in *o*-dichlorobenzene, the 2-allylphenols were partly converted to their respective 2-methylcoumarans.

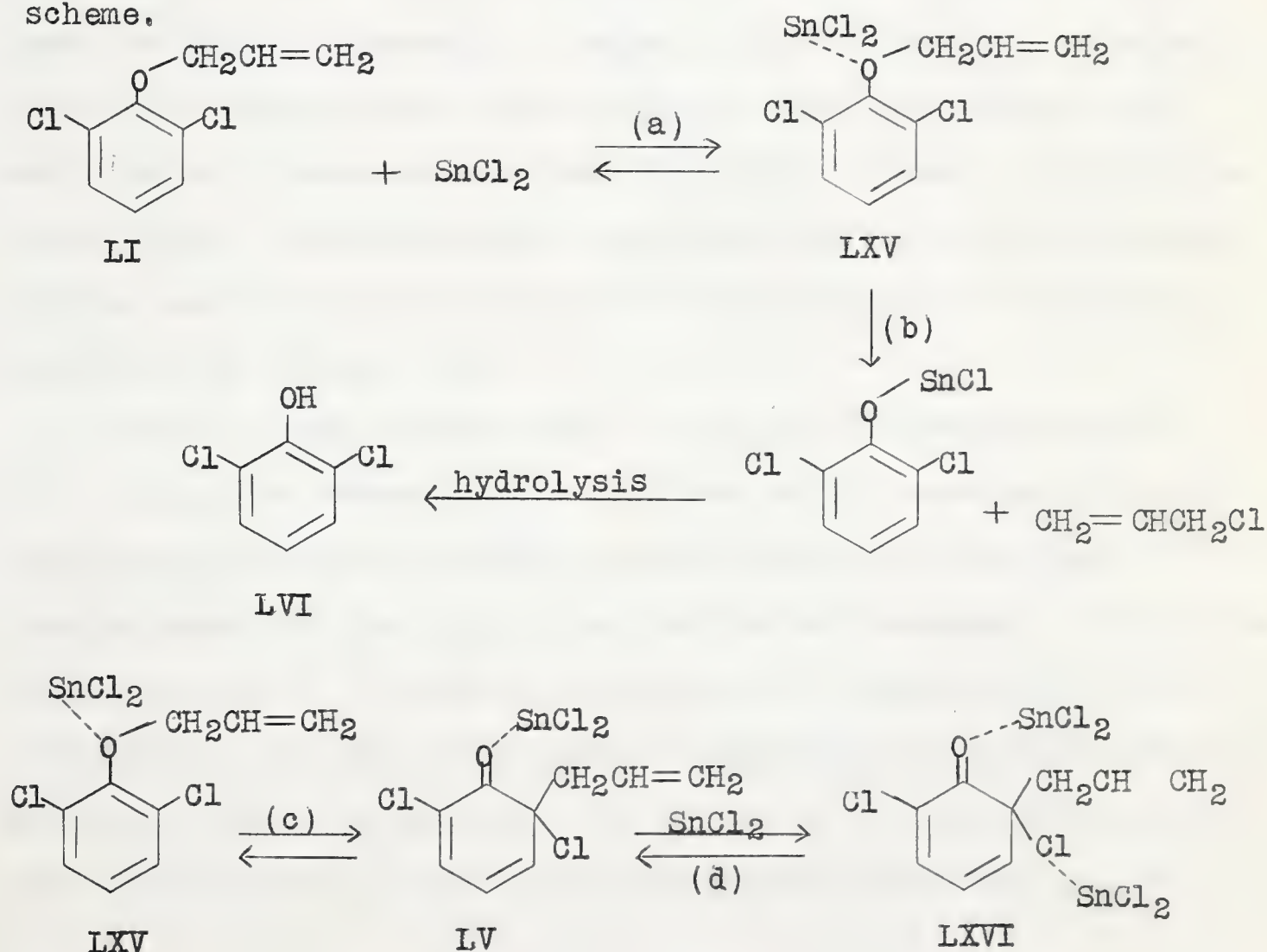
b. A considerable portion of the stannous chloride remained undissolved.

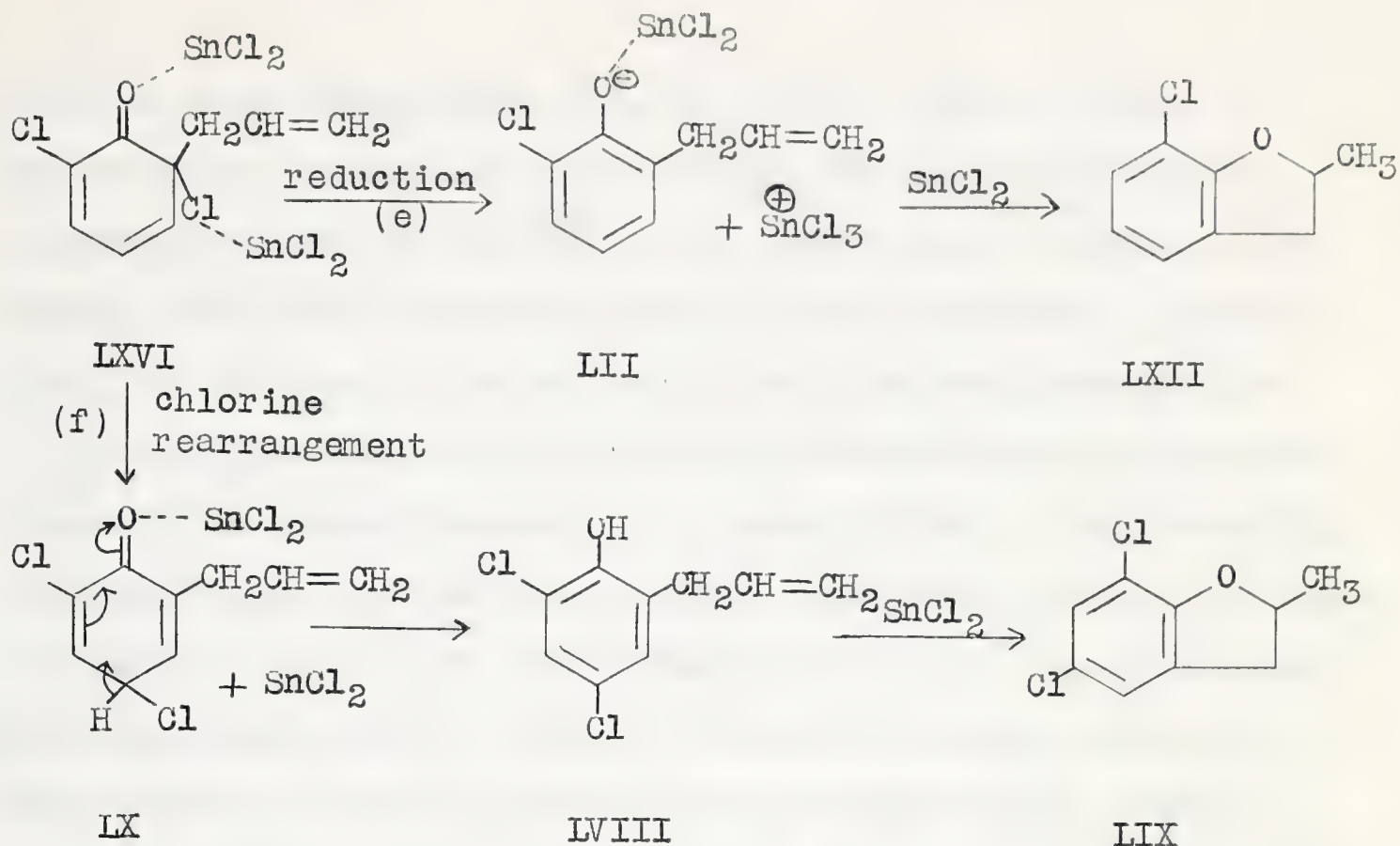
c. Nearly all the stannous chloride dissolved.

(ii) Halogen Migration and Reductive Removal

Both the reduction product 2-allyl-6-chlorophenol and the halogen migration product 2-allyl-4,6-dichlorophenol were formed during the stannous chloride-promoted rearrangement of allyl 2,6-dichlorophenyl ether, the former in somewhat larger amount in the first six hours of reaction but in relatively lesser amounts by the end of the reaction. It is possible that the accumulating stannic chloride from the reduction process could be responsible for the increasing proportion of migration product as compared with the reduction product as the reaction progressed.

The formation of the various products in the rearrangement of allyl 2,6-dichlorophenyl ether in the presence of stannous chloride can be summarized by means of the following reaction scheme.





The catalysis by stannous chloride in this reaction must have involved the formation (route a) of the stannous chloride-allyl 2,6-dichlorophenyl ether complex (LXV) which then, to a small extent, underwent cleavage (route b) to form 2,6-dichlorophenol (LVI). Simultaneously and preferentially, there occurred intramolecular rearrangement of the complex (LXV), via route c, to afford the dienone (LV).

The fact that rearrangement of allyl 2,6-dichlorophenyl ether in o-dichlorobenzene in the presence of stannous chloride produced no 4-allyl-2,6-dichlorophenol resulting from para rearrangement of the allyl group, while rearrangement of the ether in the absence of the metal halide, under otherwise identical conditions, gave para rearrangement exclusively (compare sections A and B of Table V, page 93) must mean that at the dienone stage (LV) the presence of the stannous chloride was sufficient to

cause reaction exclusively with the allylic chlorine atom by forming a complex such as LXVI in which the stannous chloride is associated with the chlorine atom (route d). The associated species (LXVI) then underwent two different reactions. In the first, the stannous chloride reductively removed (step e) the allylic chlorine to form the reduction product 2-allyl-6-chlorophenol (LII). Simultaneously, and competitively, there occurred a stannous chloride-assisted chlorine migration (route f), forming the dienone (LX), which, upon aromatization gave the 2-allyl-4,6-dichlorophenol (LVIII). Both of the o-allylphenols (LII and LVIII) were converted in part to the corresponding 2-methylcoumarans (LXII and LIX, respectively), by stannous chloride-promoted ring closure.

The possible mechanisms involved, and the manner in which the assistance by stannous chloride takes place, in the halogen migration step (route f) will be discussed later.

The results obtained in our study concerning the effect of stannous chloride on the rearrangement of allyl 2,6-dichlorophenyl ether are somewhat different in character from those reported by Carlin and co-workers (56) regarding the Fischer cyclization of 2,6-dichlorophenylhydrazones in the presence of stannous chloride. While, as noted earlier, the latter authors isolated only products (7-chloroindoles) resulting from reductive chlorine elimination, our work shows that chlorine migration, as well as reduction, can occur during the stannous chloride-promoted rearrangement of allyl 2,6-dichlorophenyl ether.

Since Carlin et. al. (56) used a large excess of stannous

chloride in their reactions, the possibility that an excess of this reagent in our work might increase the amount of reduction product was examined. The solubility of stannous chloride in o-dichlorobenzene is quite limited, hence relatively dilute solutions of reactants were employed in this experiment. A mixture of 1.25 g. (0.006 mole) of allyl 2,6-dichlorophenyl ether and 2.5 g. (0.012 mole) of stannous chloride (nearly all of which went into solution) in 125 ml. of o-dichlorobenzene, when heated at 150-155° for 24 hours, gave only two products, the reduction product 2-allyl-6-chlorophenol and the halogen migration product 2-allyl-4,6-dichlorophenol (37% and 63% respectively, section C of Table V, page 93). Thus, an increase in the proportions of stannous halide, rather than increasing the amount of reduction product, actually enhanced the proportion of halogen migration (compare sections A and C, Table V, page 93). Although these results are in apparent contrast to the findings of Carlin, Wallace and Fisher (56), it should be noted that these authors added their hydrazones to an excess of fused (260°) stannous chloride and such vigorous conditions might well account for their failure to isolate any dihalogenated indoles.

4. Possible Mechanisms for Halogen Migration in the Zinc Halide-Catalyzed Rearrangement of Allyl 2,6-Dihalophenyl Ethers

Before discussing the results obtained from further phases of our work, it may be advantageous to present the various mechanisms which could be involved in the zinc halide-promoted halogen migration which occurs during the zinc halide-catalyzed

rearrangement of allyl 2,6-dihalophenyl ethers, in order that the results obtained from these further studies, as well as those previously presented, may be discussed in terms of the proposed mechanisms.

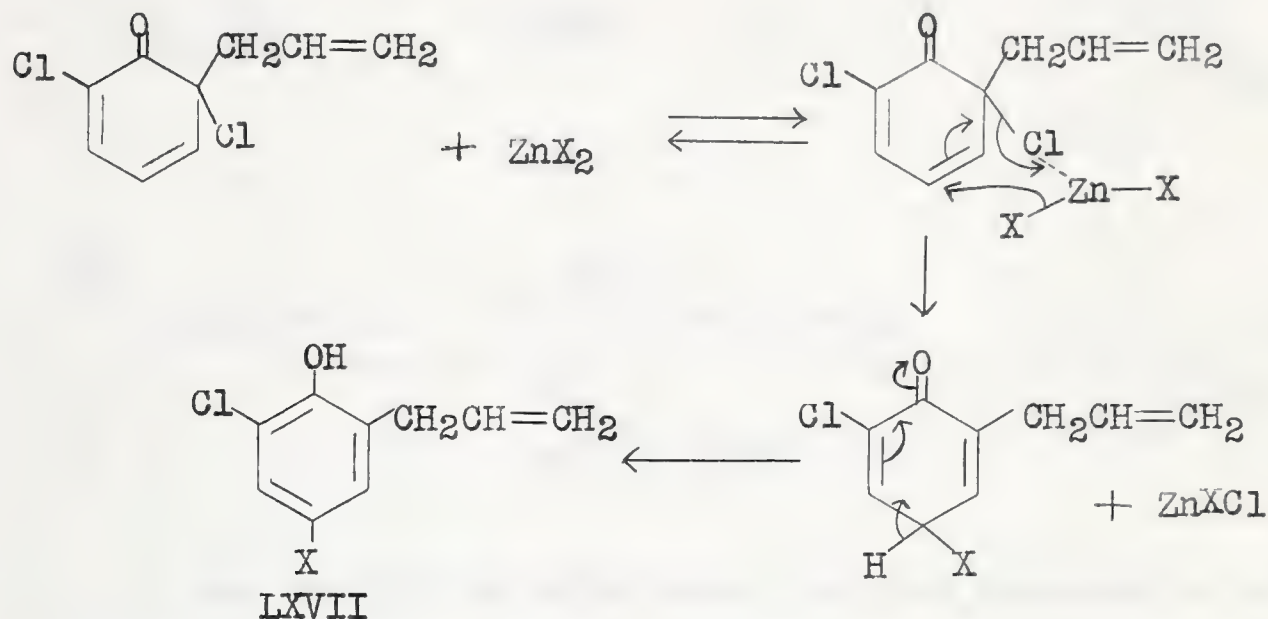
Since the halogen rearrangement occurs at the dienone intermediate stage of the reaction, consideration need be given only to the possible pathways, starting from this stage. For reasons of clarity and convenience the possible routes are discussed separately, and are demonstrated by use of the dichloro compound as the starting ether along with a generalized zinc halide (ZnX_2) formulation.

The state of the zinc halides under the conditions of our reactions is not certain. In an organic solvent which only partially dissolves the zinc halides, as is the case in our reactions, there might exist a mixture of monomeric, dimeric, and polymeric aggregations, with the dimeric and higher aggregate species possibly existing in part, for example, as $\text{ZnX}^+\text{ZnX}_3^-$. Due to the lack of precise information the designation ZnX_2 is used for simplicity.

Mechanism A

Since, as discussed previously, the results from the zinc chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether, as well as those from the rearrangement of this ether in the presence of stannous chloride, indicated that there occurred an association of the metal chloride with the allylic halogen of the dienone intermediate, the halogen migration in the zinc halide-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether

might occur via a six-centered cyclic arrangement involving the allylic chlorine, the Lewis acid, and the para position of the aromatic nucleus. This pathway, which is illustrated below, can, for obvious reasons, be conveniently referred to as a zinc halide bridge mechanism.

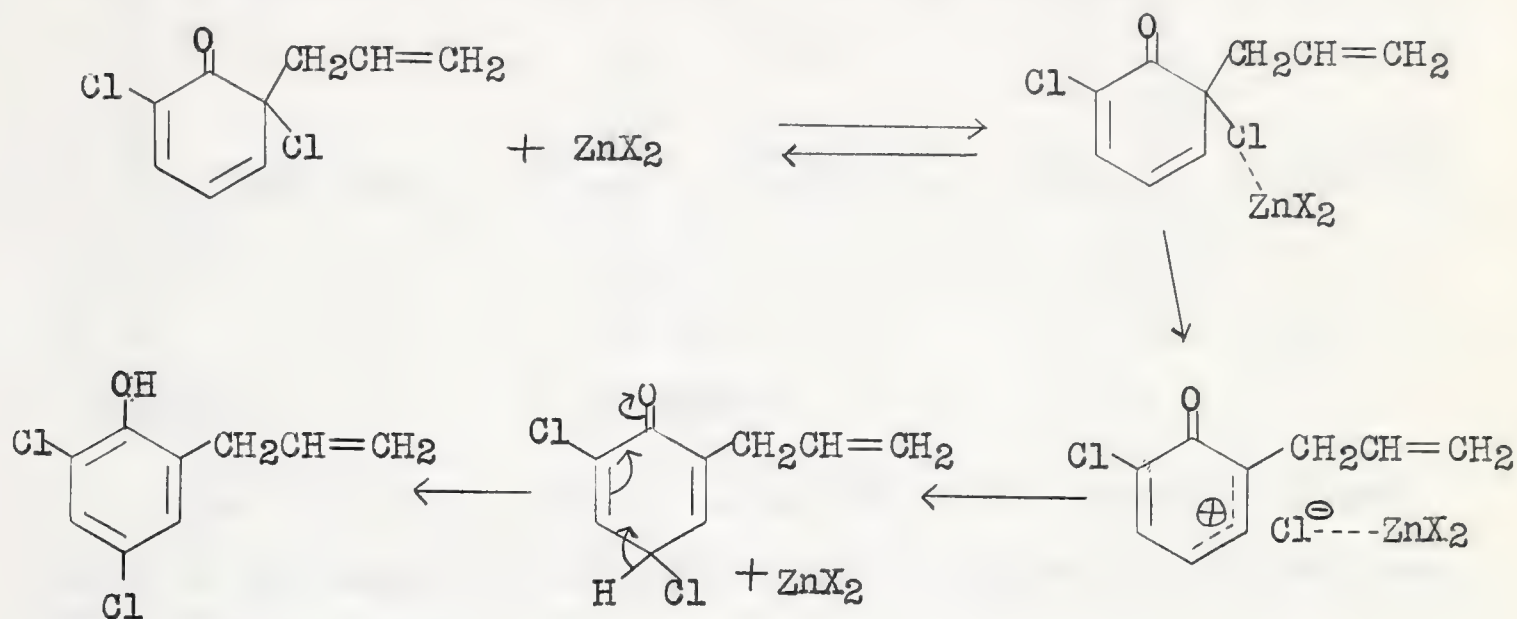


It can readily be seen that, if this mechanism were 100% operative, replacement of zinc chloride ($X=Cl$) by zinc bromide ($X=Br$) would lead to the formation of 2-allyl-4-bromo-6-chlorophenol (LXVII, $X=Br$) or, in part, its corresponding 2-methylcoumaran. As the reaction progressed, however, the species $ZnXCl$ ($X=Br$) would accumulate, which could then result in the formation of 2-allyl-4,6-dichlorophenol, the amount depending upon the relative quantity of $ZnXCl$ in solution and the comparative reactivity of the two halogens.

Mechanism B

Another possibility for the manner of halogen migration in these reactions is that of Lewis acid-promoted ionization of the allylic carbon-halogen bond in the dienone intermediate to create

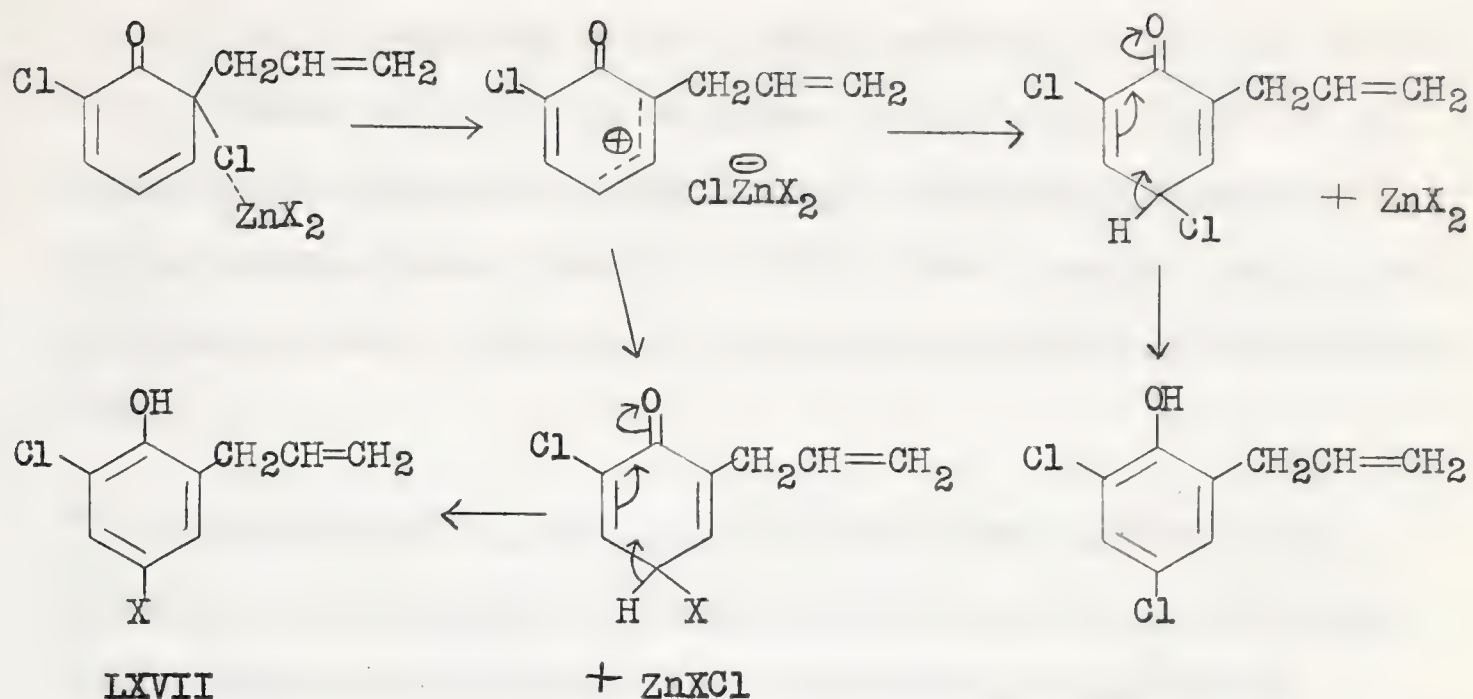
a tight ion pair which could then collapse to form 2-allyl-4,6-dichlorophenol (see below) in a manner somewhat similar to that which occurs in the purely thermal rearrangement of allyl 2,6-dichlorophenyl ether in a polar reaction medium.



It can readily be understood that the association of the Lewis acid with the allylic chlorine atom would result in much more facile ionization of the already relatively weak allylic, tertiary carbon-chlorine bond, and thus promote the halogen migration. This mechanism would result exclusively in the formation of the 2-allyl-4,6-dichlorophenol even in the presence of zinc bromide (X=Br).

Mechanism C

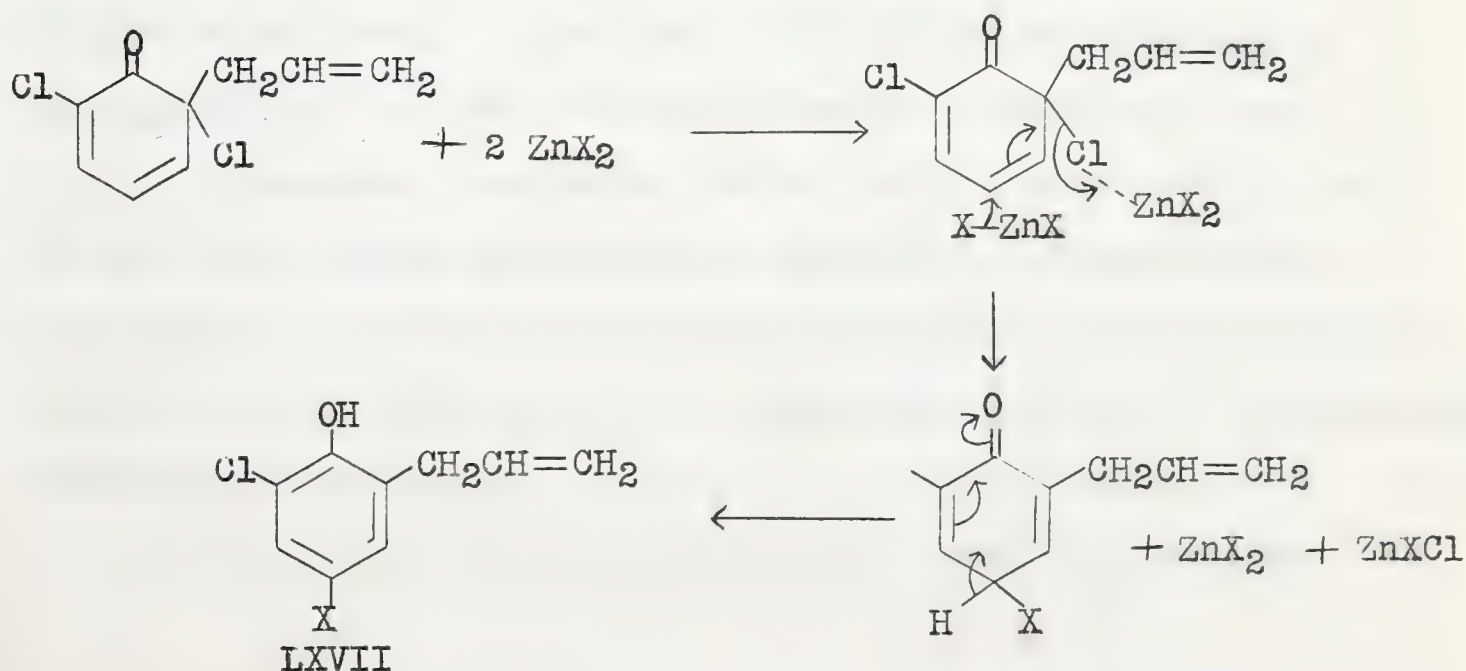
Mechanism B might be modified, under appropriate conditions, by the formation of a species such as ZnClX2^-, which could then cause substitution at the para position by X^- or Cl^-, as shown below. This mechanism would result in the formation of halogen migration product, 2-allyl-4,6-dichlorophenol, as well as halogen substitution product (LXVII).



The difference between mechanism B and Mechanism C lies only in the degree of separation of the migrating halogen from the organic moiety.

Mechanism D

In addition to the three routes described above, halogen rearrangement might be accomplished by an S_N2' mechanism (57), involving attack by a second zinc halide molecule at the C_4 position, with (or possibly without) the assistance of the Lewis acid in the ionization of the allylic carbon-halogen bond.



If this mechanism were largely operative, the application of zinc bromide ($X=Br$) as catalyst would again result in the predominant formation of the bromine substitution product 2-allyl-4-bromo-6-chlorophenol (LXVII, $X=Br$), and/or its corresponding 2-methylcoumaran, as the product of halogen rearrangement.

5. The Rearrangement of Allyl 2,6-Dichlorophenyl Ether in the Presence of Anhydrous Zinc Bromide and of Allyl 2,6-Dibromophenyl Ether in the Presence of Anhydrous Zinc Chloride

In an effort to determine whether all or some of the schemes proposed in the preceding section contribute in the formation of 2-allyl-4,6-dihalophenols in the zinc halide-catalyzed rearrangement of allyl 2,6-dihalophenyl ethers, the rearrangement of allyl 2,6-dichlorophenyl ether was carried out in the presence of anhydrous zinc bromide. As well, allyl 2,6-dibromophenyl ether was rearranged in the presence of anhydrous zinc chloride. A high proportion of 2-allyl-4,6-dichlorophenol in the first case and of 2-allyl-4,6-dibromophenol in the second would favor allylic halogen migration according to mechanism B (page 99). On the other hand, a high yield of the halogen exchange or substitution products 2-allyl-4-bromo-6-chlorophenol and 2-allyl-6-bromo-4-chlorophenol respectively, would lend support to the S_N2' scheme (mechanism D, page 101). The occurrence of both halogen substitution and halogen migration products could arise from the intervention of mechanisms C or A or a combination of mechanisms B and D.

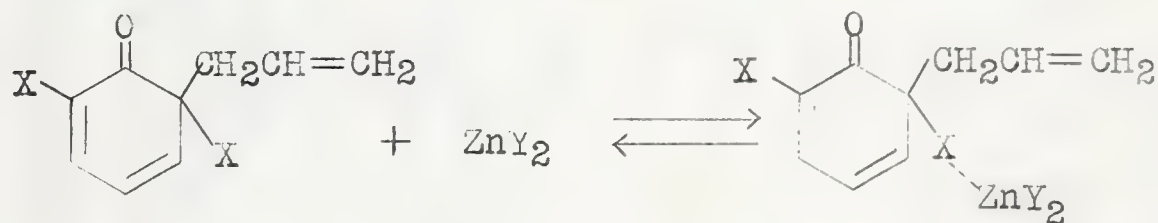
The results obtained from the zinc bromide-catalyzed

rearrangement of allyl 2,6-dichlorophenyl ether are summarized in Table VI, page 104, while those derived from the zinc chloride-catalyzed rearrangement of allyl 2,6-dibromophenyl ether are shown in Table VII, page 105.

Before the results of these studies are discussed in terms of the proposed mechanistic schemes, a number of general observations should be made concerning the information given in Tables VI and VII.

(i) No para Rearrangement of the Allyl Group

In neither case was there any indication of the formation of 4-allyl-2,6-dihalophenol, the product found in predominant amount in the purely thermal rearrangement under similar conditions. Apparently, as in the case of the zinc chloride and the stannous chloride-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether, the presence of the Lewis acid was sufficient to cause, at the dienone stage, reaction exclusively with the allylic halogen atom, thus indicating that, in every case, association of the Lewis acid with the halogen atom had occurred (see below).



(ii) Little or no Reductive Removal of Halogen

The zinc bromide-catalyzed rearrangement of the allyl 2,6-dichlorophenyl ether (Table VI, page 104) showed no evidence of reductive removal of the chlorine atom, since no 2-allyl-6-chlorophenol was formed. On the other hand, approximately 3% of the

TABLE VI

The Zinc Bromide-Catalyzed Rearrangement of Allyl 2,6-Dichlorophenyl Ether
in Nitrobenzene Solution

(Concentration of ether: 0.15 mole of ether in 1 mole of nitrobenzene.
Molar ratio of zinc bromide to ether = 2:1^a)

Reaction Time and Temperature ^b	Composition of Reaction Mixture ^c (%)				Ratio of Bromine Substitution to Chlorine Migration ^d
	2,6-Dichloro-phenol	2-Allyl-4,6-dichloro-phenol	5,7-Dichloro-2-methylcoumaran	2-Allyl-4-bromo-6-chloro-phenol	5-Bromo-7-chloro-2-methylcoumaran
100-110° 200 hr.	16	30	4	45	5 1.5
130-135° 28 hr.	28	21	12	24	15 1.2
30 hr.	40	7	20	9	24 1.2
26 hr. ^e	47	Trace	23	Trace	30 1.3
140-145° 18 hr.	47	Trace	24	Trace	29 1.2
18 hr.	51	Nil	23	Nil	26 1.1
150-155° 12 hr.	52	Nil	23	Nil	25 1.1
12 hr.	55	Nil	21	Nil	24 1.1

a. Not all of the zinc bromide dissolved.

b. Time of reaction in each case was sufficient for complete disappearance of the original ether.

c. In separate test, products were found to be stable under the reaction conditions, except that the 2-allylphenols cyclized partly or completely to their respective 2-methylcoumarans.

d. The ratios are obtained by comparison of the sums of the 2-allyl-4,6-dihalophenols and 5,7-dihalo-2-methylcoumarans in each case, i.e. the sums of columns 5 and 6, divided by the sums of columns 3 and 4.

e. A drop of water was deliberately added to the reaction mixture.

TABLE VII

The Zinc Chloride-Catalyzed Rearrangement of Allyl 2,6-Dibromophenyl Ether
in Nitrobenzene Solution

(Concentration of ether: 0.15 mole of ether in 1 mole of nitrobenzene.
Molar ratio of zinc chloride to ether = 2:1^a)

Reaction Time and Temperature ^b	Composition of Reaction Mixture ^c (%)						Ratio of Chlorine	
	2,6-Di- bromo- phenol	2-Allyl- 6-bromo- phenol	7-Bromo- 2-methyl- coumaran	2-Allyl- 4,6-di- bromo- phenol	5,7-Di- bromo- 2-methyl- coumaran	2-Allyl- 6-bromo- 4-chloro- phenol	7-Bromo- 5-chloro- 2-methyl- coumaran	Bromo- Substitution to Bromine Migration ^d
130-135° 50 hr.	8	3	Nil	55	2	30	2	0.56
140-145° 26 hr.	16	2	1	38	6	31	6	0.84
150-155° 22 hr.	26	1	2	25	10	24	12	1.0

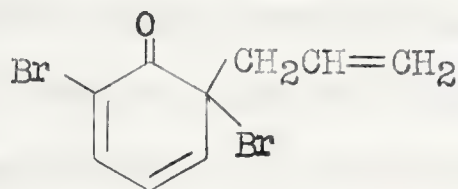
a. Not all of the zinc chloride dissolved.

b. Time of reaction in each case was sufficient for complete disappearance of the original ether.

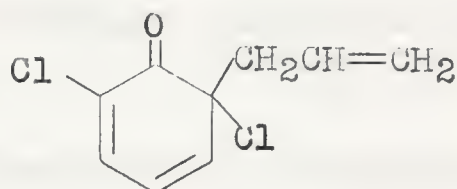
c. In separate tests, products were found to be stable under the reaction conditions, except that the 2-allylphenols were partly converted to their respective coumarans.

d. The ratios are obtained by comparison of the sums of the 2-allyl-4,6-dihalophenols and 5,7-dihalo-2-methylcoumarans in each case, i.e. the sums of columns 7 and 8, divided by the sums of columns 5 and 6.

product obtained from the zinc chloride-catalyzed rearrangement of the dibromo ether (Table VII, page 105) was the monobromo reduction product 2-allyl-6-bromophenol (and/or its corresponding 2-methylcoumaran). Thus, the allylic carbon-bromine bond in the dienone (LXVIII) is more susceptible to the competitive reductive cleavage than is the allylic carbon-chlorine bond in the dienone (LV).



LXVIII



LV

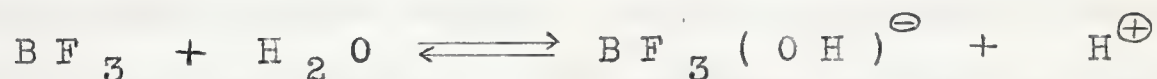
(iii) Ether Cleavage

Cleavage of the ethers to the respective 2,6-dihalophenols in each case increased with increase in reaction temperature, but was more pronounced in the zinc bromide-catalyzed reaction. Thus, for example, rearrangement of allyl 2,6-dichlorophenyl ether in the presence of zinc bromide at 140-145° produced about 50% of ether cleavage material, 2,6-dichlorophenol (Table VI, page 104), while under the same conditions, the zinc chloride-catalyzed rearrangement of allyl 2,6-dibromophenyl ether gave only 16% of 2,6-dibromophenol (Table VII, page 105).

It is noteworthy that, in contrast to the results obtained with zinc chloride as catalyst, those from the zinc bromide-catalyzed rearrangements were difficult to reproduce in duplicate reactions. Commercial anhydrous zinc bromide itself (obtained from Matheson, Coleman and Bell, Norwood, Ohio, U.S.A.), was particularly bad in this regard and therefore, before use, it was

heated to its melting point (as was done for the zinc chloride) to drive off traces of water. If one treated the zinc bromide in this way, and then allowed it to cool in a desiccator containing phosphorus pentoxide and dry nitrogen, and as well stored the desiccator in a dry box (phosphorus pentoxide) flushed with dry nitrogen and finally carried out all weighings, transfer and mixing manipulations in this dry box, considerable improvement in reproducibility was found, although the results even then were not entirely satisfactory.

Even though all the above-mentioned precautions were taken, it is possible that traces of water could be the cause of this difficulty in reproducing the results. From our observations, zinc bromide was considerably more hygroscopic than was zinc chloride. Furthermore, the addition of one drop of water to the reaction mixture containing the zinc bromide catalyst (Table VI, page 104, 36 hour run at 130-135°) increased the amount of ether cleavage. It is already known that the addition of a small amount of water to a reaction involving boron trifluoride does enhance the catalytic power of this Lewis acid, probably by production of a proton according to the reaction shown below (58-61).



Comparison of the results obtained from the zinc bromide-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether (Table VI, page 104) with those derived from the rearrangement of allyl 2,6-dibromophenyl ether in the presence of zinc chloride (Table VII, page 105) reveals that the Lewis acid, zinc bromide, was not

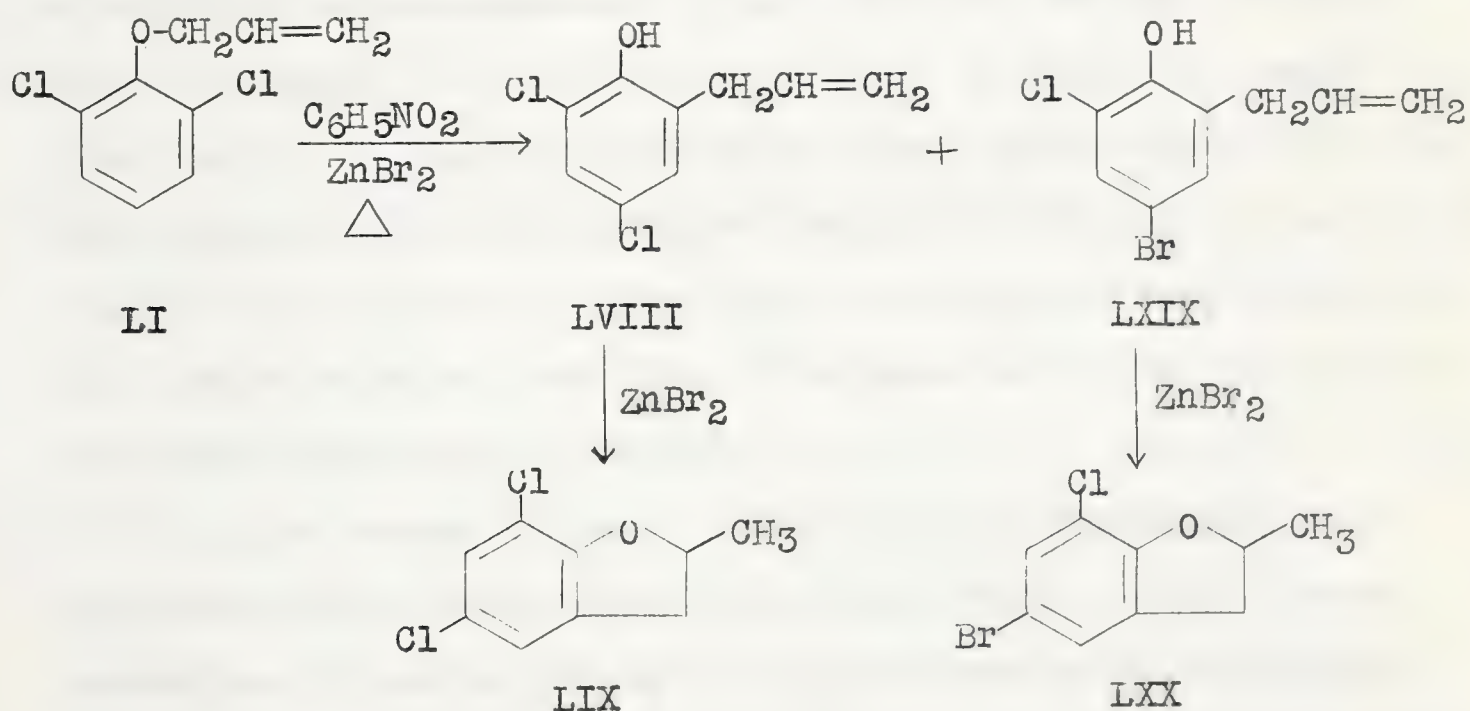
only more effective in causing ether cleavage, as noted above, but was also more efficient in promoting cyclization of the 2-allyl-4,6-dihalophenols to the corresponding 2-methylcoumarans, a distinctly acid-catalyzed reaction. It was felt that these observed phenomena might be due to the somewhat stronger Lewis acid character of the zinc bromide as compared with that of zinc chloride. Analogously, aluminum bromide is considered to be a more effective catalyst in the Friedel and Crafts reaction than is aluminum chloride (62). Furthermore, it has been shown that the electrophilicities of the boron halides toward pyridine or nitrobenzene are in the order $\text{BF}_3 < \text{BCl}_3 < \text{BBr}_3$ (63), indicating the Lewis acid strength of these halides is in the order $\text{BBr}_3 > \text{BCl}_3 > \text{BF}_3$. To our knowledge, no such comparison has as yet been reported concerning the aluminum halides, or the zinc halides, although such work has been under consideration (63).

However, if one can extrapolate the results obtained concerning the boron halides to the zinc halides, support is thus obtained for the view that zinc bromide is a stronger Lewis acid than is zinc chloride. The greater solubility of the zinc bromide in nitrobenzene, as observed in our work, indicates greater coordinating power with the solvent. On the other hand, the greater solubility of the bromide in nitrobenzene, as well as that of aluminum bromide in benzene in the Friedel and Crafts reaction (62) as compared with the solubilities of the corresponding chlorides, could well explain the greater catalytic effect observed. The limited amount of information available precludes any definite conclusion as yet concerning the cause of the greater activity

observed in the case of the zinc bromide.

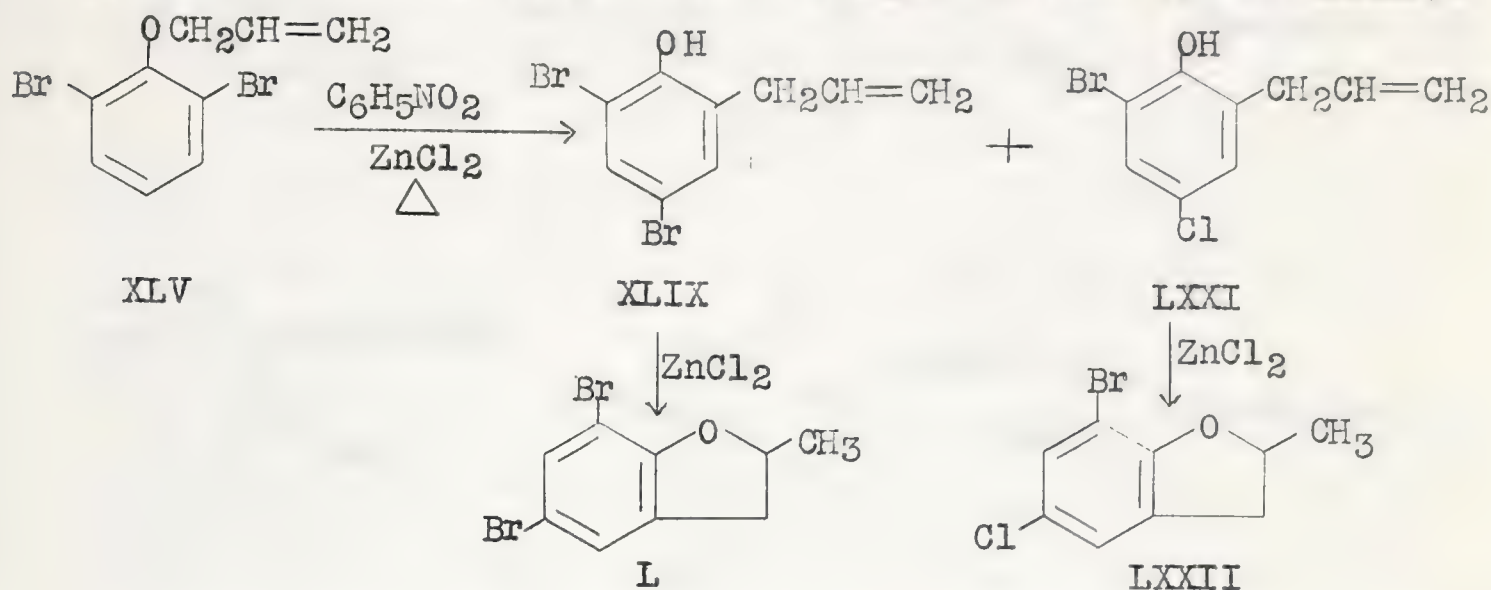
(iv) Simple Allylic Halogen Migration in Competition with Halogen Substitution by Halide Ion

The results summarized in Tables VI and VII, pages 104 and 105 respectively, show that halogen substitution as well as halogen migration occurred during the zinc halide-catalyzed rearrangement of allyl 2,6-dihalophenyl ethers. Thus, when allyl 2,6-dichlorophenyl ether (LI) was caused to rearrange in nitrobenzene in the presence of zinc bromide, there was formed in addition to the product of chlorine migration, 2-allyl-4,6-dichlorophenol (LVIII), a considerable amount of the bromine substitution product, 2-allyl-4-bromo-6-chlorophenol (LXIX), both of which were converted in part, or completely, to their corresponding 2-methylcoumarans (LIX and LXX respectively).



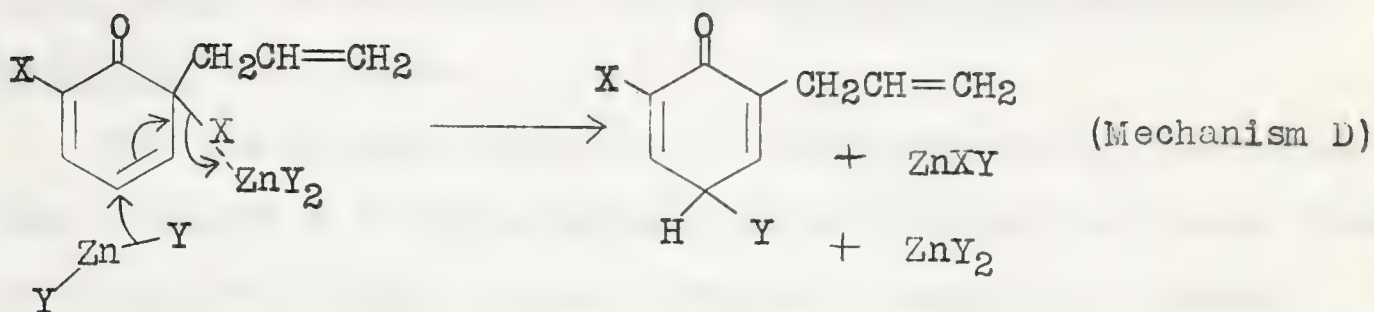
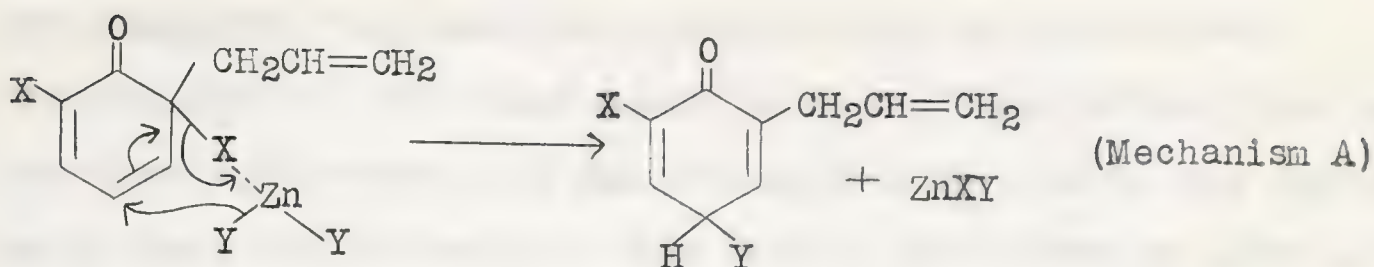
Similarly, the zinc chloride-catalyzed rearrangement of allyl 2,6-dibromophenyl ether (XLV) afforded 2-allyl-4,6-dibromo-

phenol (XLIX) and 2-allyl-6-bromo-4-chlorophenol (LXXI), along with some of their respective 2-methylcoumarans (I and LXXII).

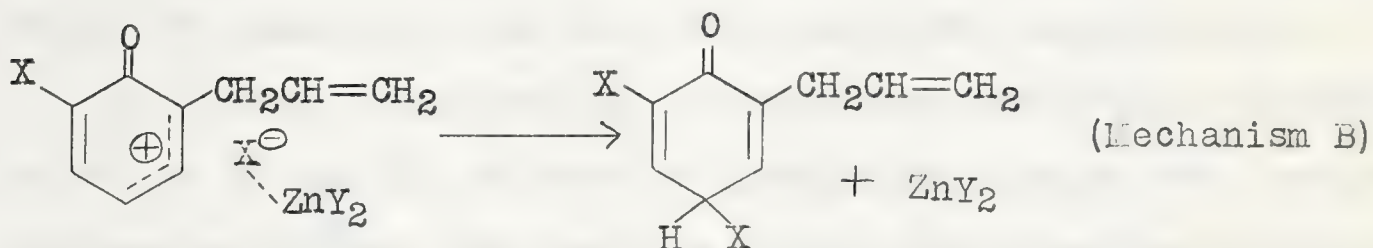


It was found that the ratio of halogen substitution to halogen migration increased with temperature in the zinc chloride-catalyzed rearrangement of allyl 2,6-dibromophenyl ether, but decreased slightly in the zinc bromide-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether (compare the last column of Table VI, page 104 with the last column of Table VII, page 105). Also, under the same conditions at lower temperatures (130-135°) more bromine (from zinc bromide) replaced chlorine in the latter reaction than chlorine (from zinc chloride) replaced bromine in the former reaction, but this difference was nearly eliminated at higher temperatures (150-155°).

At this stage, it is clearly seen that predominant substitution, which must occur if the zinc halide bridge concept (mechanism A) and/or the $\text{S}_{\text{N}}2'$ route (mechanism D) were 100% operative, did not take place. Hence halogen rearrangement can occur only partially, if at all, by one or both of these processes.

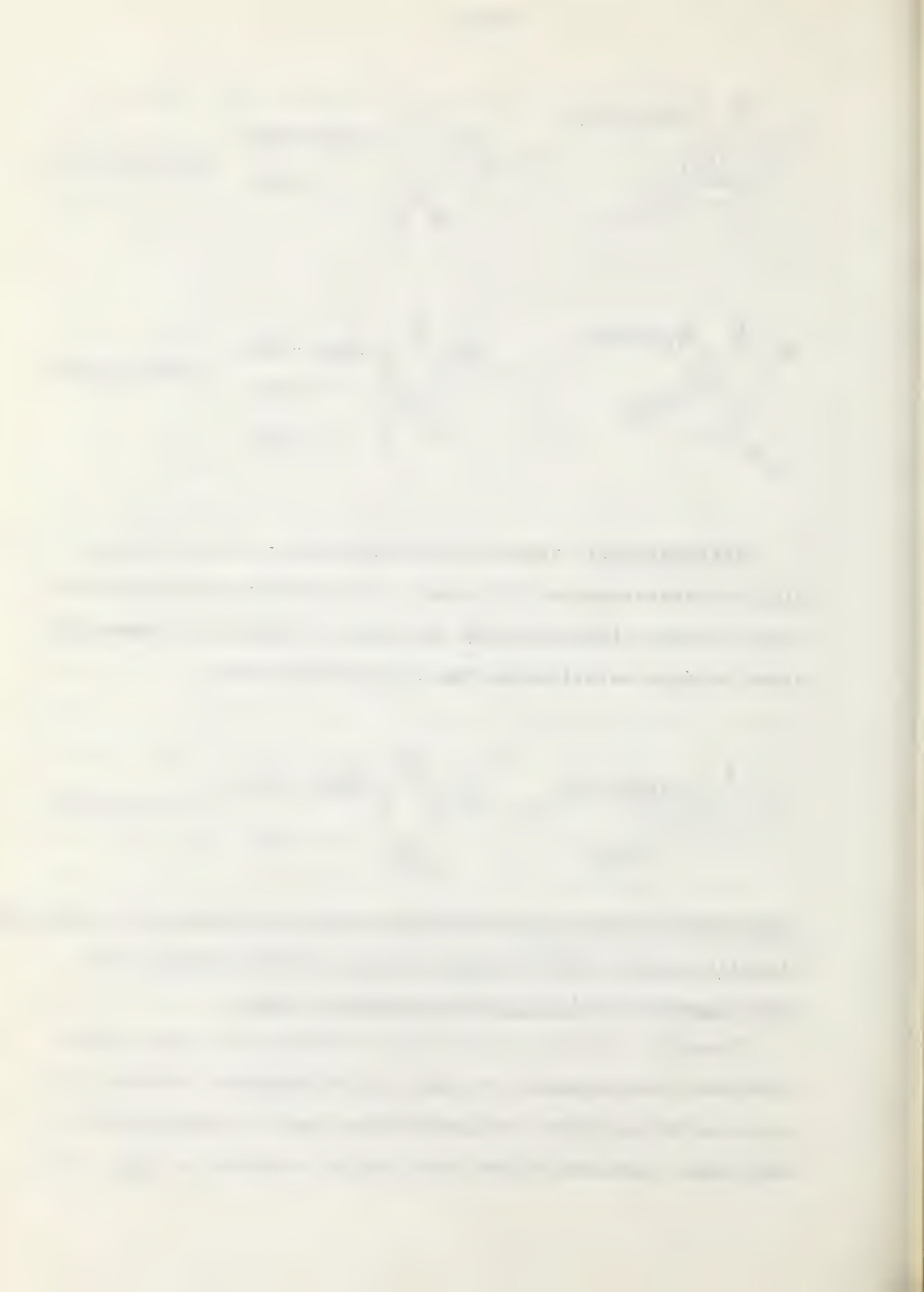


Alternatively, simple allylic migration of the halogen with the assistance of the zinc halide and involving a rather tight ion pair (mechanism B) was also not completely operative, since halogen substitution was quite substantial.



Conclusions concerning the Possible Mechanisms Involved in Halogen Migration and/or Substitution in the Zinc Halide-Catalyzed Rearrangement of Allyl 2,6-Dihalophenyl Ethers

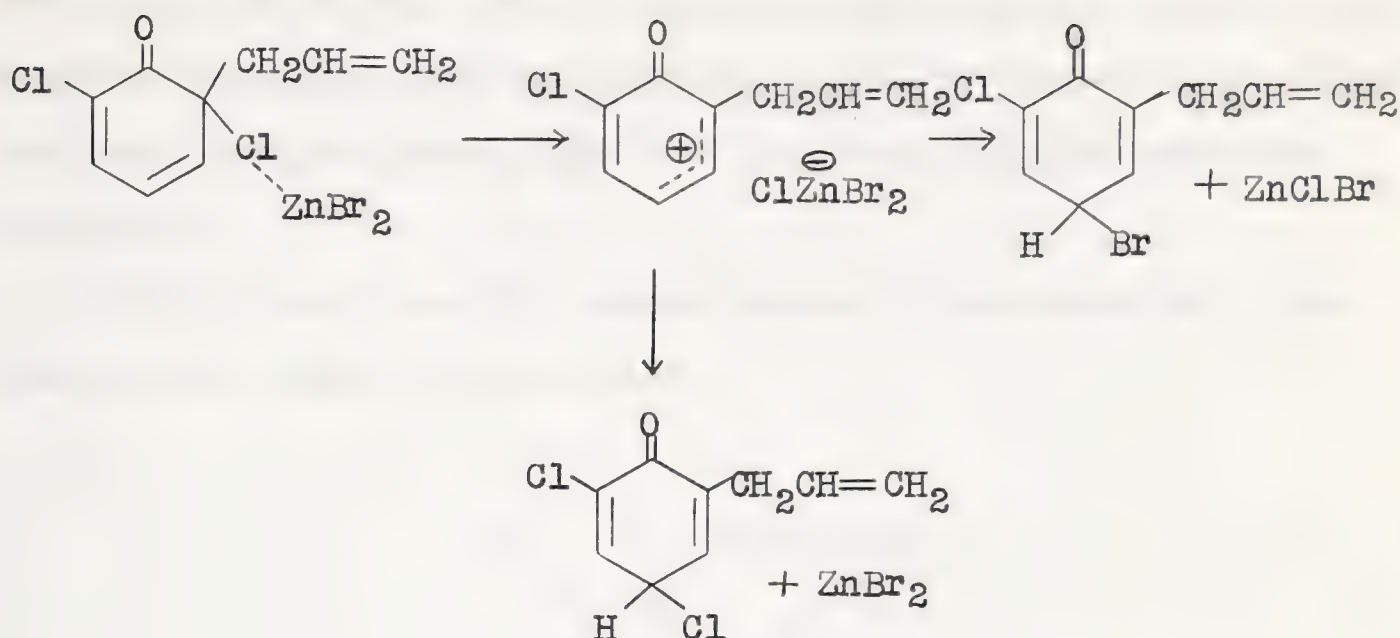
From the results of our work concerning the zinc halide-catalyzed rearrangement of allyl 2,6-dihalophenyl ethers, it is quite obvious that the Lewis acids exert a marked control over these reactions since there was no evidence of para allyl



rearrangement, the reaction normally found in the thermal rearrangements. This must mean, as pointed out before, that in the zinc halide-catalyzed rearrangements, to control the reaction as it does, one molecule of zinc halide must first be associated with the allylic halogen of the dienone intermediate stage in every case. Subsequently, halogen substitution and halogen migration take place.

The use of zinc chloride as a catalyst for the rearrangement of allyl 2,6-dichlorophenyl ether resulted in a high yield of 2-allyl-4,6-dichlorophenol (Table I, page 67). However, whether this occurred by allylic halogen "migration", or by "substitution" at the para position by a halogen from the zinc chloride catalyst could not be ascertained. The results from the zinc bromide-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether and from the zinc chloride-catalyzed rearrangement of allyl 2,6-dibromophenyl ether are considerably more informative (Table VI, page 104, and Table VII, page 105 respectively).

An attempt might be made to interpret the results presented in Tables VI and VII in terms of mechanism C (page 100) involving the species $\text{Cl}\overset{\ominus}{\text{Zn}}\text{Br}_2$ (in the case of the zinc bromide-catalyzed reaction) and $\text{Br}\overset{\ominus}{\text{Zn}}\text{Cl}_2$ (in the case of the zinc chloride-catalyzed reaction). Thus, for example, in the rearrangement of allyl 2,6-dichlorophenyl ether in the presence of zinc bromide, the carbonium ion could abstract a halide ion from the species $\text{Cl}\overset{\ominus}{\text{Zn}}\text{Br}_2$, either a chloride ion to form the dichloro "migration" product, or a bromide ion to form the chloro bromo "substitution" product, as illustrated below.



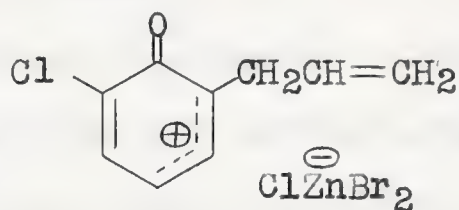
To assist us in evaluating this mechanism, excerpts from Tables VI and VII are arranged as shown below.

Temperature of Reaction	Ratio of 4-Bromo Product to 4-Chloro Product	
	For Zinc Bromide- Catalyzed Reaction	For Zinc Chloride- Catalyzed Reaction
100-110°	1.5	---
130-135°	1.2-1.3	1.8
140-145°	1.1-1.2	1.2
150-155°	1.1	1.0

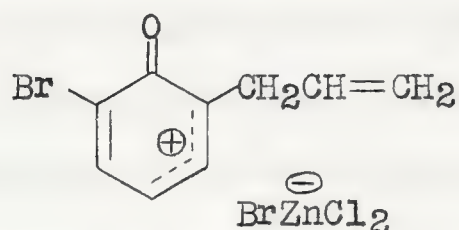
In both the zinc bromide and the zinc chloride-catalyzed reactions, the ratio of the 4-bromo product to the 4-chloro product decreased from a value greater than 1.0 (1.5 and 1.8, respectively) as the reaction temperature increased, until at 150-155° the ratio was nearly 1.0 in both cases. That is, at 150-155°, there were formed nearly equal amounts of 2-allyl-4-

bromo-6-chlorophenol and 2-allyl-4,6-dichlorophenol in the zinc bromide-catalyzed reaction and of 2-allyl-6-bromo-4-chlorophenol and 2-allyl-4,6-dibromophenol in the zinc chloride-catalyzed reaction.

If the reactions did indeed proceed via mechanism C, one would expect that in the case of



abstraction of bromide ion should be considerably easier than abstraction of chloride ion. Furthermore, at least during the first portion of the reaction, twice as many bromide ions than chloride ions are available. Hence one would expect a larger proportion of 2-allyl-4-bromo-6-chlorophenol as compared with 2-allyl-4,6-dichlorophenol. For the zinc chloride-catalyzed reaction,

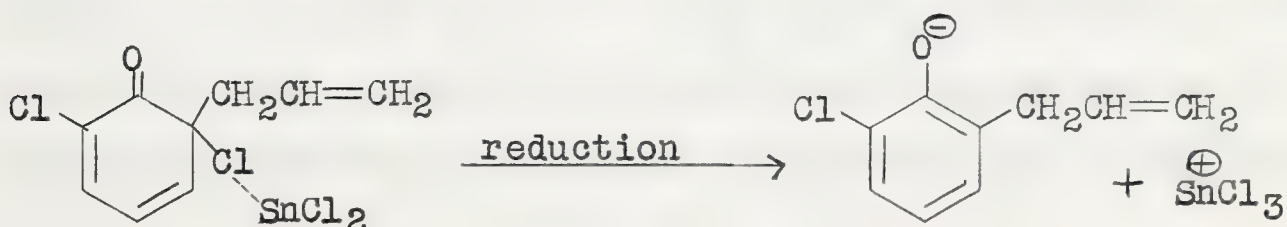


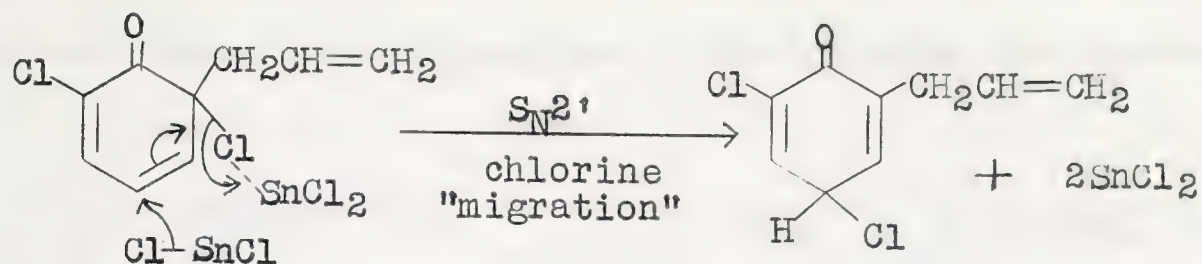
one would expect less bromide ion abstraction than in the above case. However, according to the figures in the abbreviated table above, at 130-135° the ratio of 4-bromo product to 4-chloro product was greater for the zinc chloride-catalyzed reaction (1.8) than for the zinc bromide-catalyzed reaction (1.2-1.3). This should be the reverse if the relative nucleophilicity and

the relative amounts of chloride ion and bromide ion are considered. Even at higher temperatures the zinc bromide-dichloro ether reaction would be expected to afford a larger than 1:1 ratio of the 4-bromo to 4-chloro compound. The difference between the nucleophilities of the bromide and chloride ions at higher temperatures would decrease, but the likelihood that they would be equal is doubtful.

Thus, intervention of mechanism C (page 100) as the only route for halogen migration and substitution in these reactions is very doubtful, although some contribution by this scheme might occur.

The rearrangement of allyl 2,6-dichlorophenyl ether in the presence of stannous chloride offers some assistance in the choice of a mechanism. In this reaction, the formation of a greater amount of halogen "migration" product, 2-allyl-4,6-dichlorophenol, as compared with the reduction or halogen removal product, 2-allyl-6-chlorophenol, rather than the reverse when the proportion of stannous chloride to dichloro ether was increased (Table V, page 93) can be taken as support for the participation of a second molecule of stannous chloride in an S_N2' reaction. Thus, considering the dienone stage, the S_N2' reaction would be in competition with that of reduction, as shown below. One would not expect a markedly greater extent

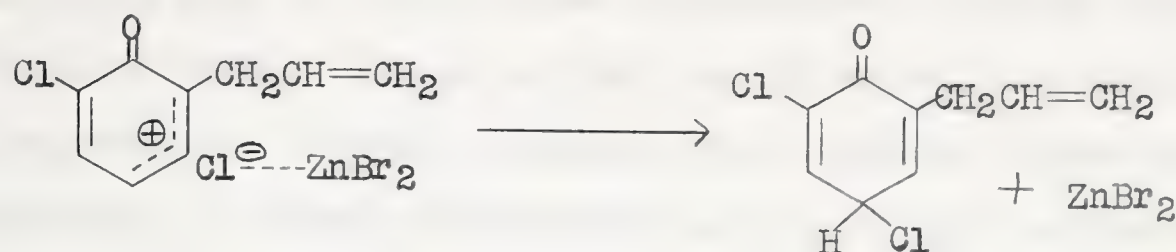




of reduction with a higher proportion of stannous chloride present, since it appears that there is already one molecule of stannous chloride preferentially associated with the allylic halogen. The presence of a second molecule in the same vicinity should not enhance the reducing power of the first molecule, but it could enter the reaction as a nucleophilic agent, attacking the allylic C₄ carbon by an S_N2' pathway, thus increasing the amount of halogen "migration" relative to reduction. Hence the S_N2' mechanism as a contributing scheme for halogen rearrangement has some support.

The results obtained from the zinc bromide-catalyzed rearrangement of allyl 2,6-dichlorophenyl ether (Table VI, page 104) show that at 100-110° the ratio of halogen substitution product to halogen migration product was 1.5. But as the temperature increased this ratio decreased, becoming 1.2-1.3 at 130-135° and 1.1 at 150-155°. The information obtained from the stannous chloride-dichloro ether reaction indicated that participation of the Lewis acid in an S_N2' type of reaction is possible. This would be even more likely with zinc bromide due to the greater nucleophilicity (64) of the bromide ion as compared with

that of the chloride ion. Hence, a competition is envisaged between the allylic migration of the chlorine via mechanism B



and substitution via mechanism D.

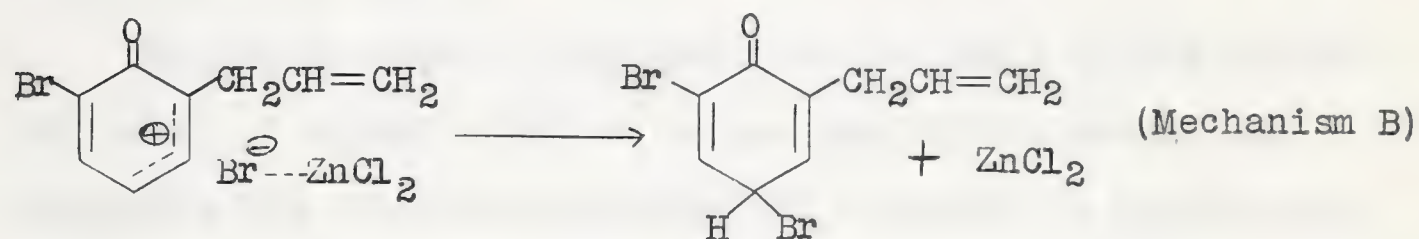


It is also possible that bromine substitution at C₄ could occur in part via the zinc halide bridge mechanism (mechanism A, page 98), and/or by mechanism C (page 100).

Higher reaction temperatures apparently facilitated the breaking of the allylic carbon-chlorine bond and hence a relatively greater contribution of mechanism B occurred, decreasing the ratio of bromine substitution to chlorine migration.

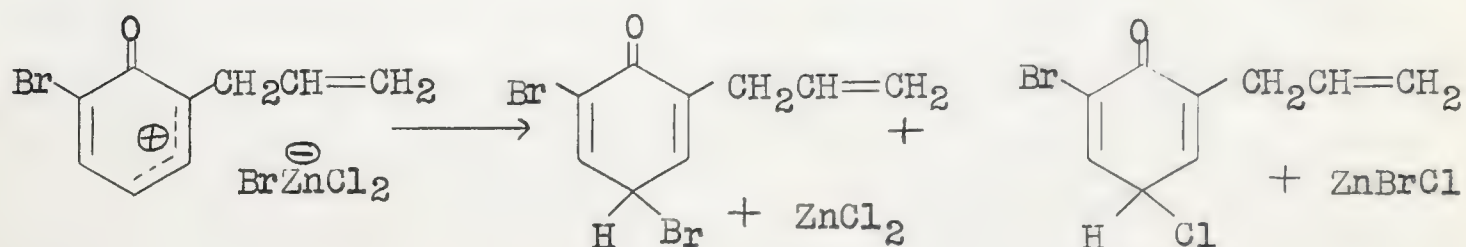
The rearrangement of allyl 2,6-dibromophenyl ether in the presence of zinc chloride at 130-135° gave a ratio of bromine migration product to chlorine substitution product of 1.8 (Table VII, page 105). That is, nearly twice as much bromine migration occurred as compared with chlorine substitution. As the reaction temperature increased, however, this ratio decreased, becoming 1.0 at 150-155°. One might expect that with the dibromo ether

the allylic carbon-bromine bond of the dienone intermediate would be more readily ionized than would be the allylic carbon-chlorine bond of the dienone intermediate obtained from the dichloro ether. Hence, already at relatively low reaction temperatures, bromine migration via mechanism B was quite prominent. Attack of chloride ion via an S_N2' mechanism was



less competitive due to its lower nucleophilicity as compared with that of the bromide ion.

Higher reaction temperatures could cause the formation of the species $\text{Br}^{\ominus}\text{ZnCl}_2$, in which the bromide ion has been removed from the tight ion pair arrangement of mechanism B. This could then result in attack by chloride ion or bromide ion on the allylic group at C_4 , as indicated below. Since there is a greater proportion of chlorine than bromine in the species $\text{Br}^{\ominus}\text{ZnCl}_2$ and since at higher temperatures some decrease in the difference of reactivity of chloride ion and bromide ion would be expected, the proportion of bromine migration to chlorine substitution should decrease, as was observed.



6. Conclusion

The results obtained from the zinc halide-catalyzed rearrangement of allyl 2,6-dihalophenyl ethers indicate that, at the dienone stage of these reactions, there occurred an association of the zinc halide with the allylic halogen of the dienone. Subsequently there occurred halogen migration and halogen substitution.

For these complex reactions, on the basis of the results obtained, it appears that no single one of the mechanisms suggested can adequately explain the results. A postulation of a competition between the routes can be offered in which allylic halogen migration occurs with the assistance of the Lewis acid (mechanism B, page 99). Along with this there occurs halogen substitution via an S_N2' mechanism (page 101) and possibly in part by a zinc halide bridge mechanism (page 98). A contribution to the reactions could also arise from the scheme suggested in mechanism C (page 100) whereby a species such as $Zn\overset{\ominus}{X}_2Y$ is formed, which then attacks the carbonium ion to yield the C_4 -halogenated products, the amount of each depending on the statistical number of halogens (in $Zn\overset{\ominus}{X}_2Y$) and their relative nucleophilicity.

EXPERIMENTAL

All melting points and boiling points reported in this section are uncorrected.

Microanalyses were performed by the F. Pascher Micro-analytisches Laboratorium, Bonn, Germany and by C. Daesslé, Organic Microanalyses, Montreal, Canada.

1. Analyses by Gas Chromatography and Product Identification

A Burrell Model K-2 Kromo-Tog, equipped with an integrator, and with helium as carrier gas, was used for all analyses. A 2 m. column, packed with 20% Apiezon L on Gas Chrom P (60-80 mesh), afforded good separation of components into clearly resolved peaks. The column temperature depended somewhat upon the boiling points of the products, but was usually in the region of 180-220°. The flow rate of helium was approximately 100 ml. per minute for all analyses.

Analyses of carefully weighed authentic mixtures of the reaction products showed that the integrated paper areas of the peaks could be used as a direct measure of the molar compositions of the reaction mixtures.

Products were identified by comparison of their v.p.c. retention times with those of authentic samples, and/or by their isolation from the reaction mixtures, followed by comparison of their physical constants and their infrared (Perkin-Elmer Model 221) and nuclear magnetic resonance (Varian A-60) spectra with those of the authentic compounds.

2. Purification of Materials

A. Solvents

The solvents employed in our work were all commercially available and were purified by treatment with a drying agent, followed by distillation, under dry nitrogen, at atmospheric pressure, or under reduced pressure. The chart below gives a list of the solvents, along with their boiling points and the drying agent used in each case.

Solvent	Drying Agent	B.p. of Solvent/mm
Decalin	Drierite	190-191°/700
Diphenyl ether	Drierite	102-103°/3
<u>o</u> -Dichlorobenzene	Drierite	176-178°/700
Phenol	(a)	177-178°/700
Benzonitrile	Magnesium sulphate	186°/700
N,N-Diethylformamide	Magnesium sulphate	70-71°/20
Nitrobenzene	Drierite	205-206°/700
N-Methylformamide	Magnesium sulphate	75-76°/10

(a) Phenol was not dried prior to distillation.

B. Reagents

Zinc Chloride

Anhydrous granular zinc chloride (reagent grade), obtained from Fisher Scientific Company, Fair Lawn, N.J., U.S.A., was heated to its melting point in a porcelain dish to drive off traces of water. It was then allowed to cool in a desiccator containing phosphorus pentoxide and dry nitrogen. The desiccator was stored in a dry box (P_2O_5) which had been flushed with dry nitrogen. All weighings, transfer and mixing manipulations involving the Lewis acid were carried out in this dry box.

Zinc Bromide

Reagent grade zinc bromide powder obtained from Matheson, Coleman and Bell, Norwood, Ohio, U.S.A., was treated, stored and handled in a manner analogous to that described above for zinc chloride.

Lithium Chloride

Anhydrous lithium chloride reagent (Fisher Scientific Company, Fair Lawn, N.J., U.S.A.) was dried and handled as described for zinc chloride.

Stannous Chloride

The method of Stephen (65) was employed to prepare this material.

Reagent grade stannous chloride dihydrate (226 g., 1 mole), obtained from The British Drug Houses Canada Limited, Toronto, Canada, was treated with acetic anhydride (204 g., 2 moles). The dehydration was almost instantaneous, much heat was evolved, and the anhydrous salt separated. The salt was collected by filtration,

washed free of acetic acid with anhydrous ether, and then immediately placed in a desiccator under vacuum. When all the solvent was evaporated, the stannous chloride was stored in a desiccator containing P_2O_5 and nitrogen. The salt did not appear to be hygroscopic and could be preserved indefinitely in the desiccator.

3. Preparation of 2,6-Dichlorophenol

The method of Tarbell, Wilson and Fanta (66) was employed to prepare this compound.

A. Ethyl 3,5-Dichloro-4-hydroxybenzoate

To a 2-l., round-bottomed flask, equipped with an efficient reflux condenser and set up on a steam bath in a fume hood, was added 250 g. (1.5 moles) of ethyl 4-hydroxybenzoate (obtained from Eastman Organic Chemicals, Rochester, N.Y., U.S.A.) and 444 g. (266 ml., 3.3 moles) of practical grade sulphuryl chloride. The mixture was warmed on the steam bath, gently at first, until gas was no longer evolved (about 1 hour). Then 50 ml. of sulphuryl chloride was added to the reaction flask and the warming was continued until gas evolution ceased. This entire chlorination procedure required about 1.5 hours. The excess sulphuryl chloride was then removed by attaching a water pump through an empty safety flask to the reaction flask and warming the vessel on the steam bath until no evidence of vapor could be detected above the white solid in the reaction flask. Crystallization of the solid from aqueous ethanol, gave 315 g. (89%) of ethyl 3,5-dichloro-4-hydroxybenzoate hydrate, m.p. 108-111° (dec.); lit. m.p. 110-114°

(dec.) (66).

B. 3,5-Dichloro-4-hydroxybenzoic Acid

To a 2-l. round-bottomed flask equipped with a reflux condenser and set upon a steam bath was added ethyl 3,5-dichloro-4-hydroxybenzoate hydrate (315 g., 1.35 moles) and 600 ml. of Claisen's alkali (52). Saponification was brought to completion by heating on the steam bath for 1 hour. A yellow, homogeneous solution resulted, which was diluted with 400 ml. of water and then acidified by pouring it into a rapidly stirred solution of 320 ml. of concentrated hydrochloric acid and 300 ml. of water in a 4 l. beaker. After the thick, white slurry had been cooled to 0°, the solid was collected by filtration and washed twice with cold water. The filter cake was freed from as much water as possible by suction, and then was broken up and dissolved in a boiling mixture of 1 l. of ethanol and 350 ml. of water. Cooling the solution to 0° gave the first crop of crystals, weighing about 200 g. Concentration of the mother liquor to 750 ml. and cooling to 0°, afforded an additional amount of product of equal purity. After being air-dried, the white crystalline 3,5-dichloro-4-hydroxybenzoic acid weighed 250 g. (89%) and melted at 266-268°; lit. m. p. 266-268° (66).

C. 2,6-Dichlorophenol

A mixture of dry 3,5-dichloro-4-hydroxybenzoic acid (250 g., 1.2 moles) and redistilled dimethylaniline (575 g., 600 ml., 4.8 moles) was placed in a 2 l. round-bottomed flask provided with a thermometer and a short air-cooled condenser. The reaction mix-

ture was then heated slowly with a heating mantle. Evolution of gas commenced at about 130° and was vigorous at 150° . The solution was heated at $190-200^{\circ}$ for 2 hours, cooled to 0° , and poured in small portions into 600 ml. of cold (0°) concentrated hydrochloric acid, with cooling from time to time by means of an ice-water bath. The resulting mixture, after being thoroughly cooled, was extracted with three 250-ml. portions and three 100-ml. portions of ether. The combined ether extracts were washed several times with 6N hydrochloric acid and dried over anhydrous sodium sulphate. Removal of the ether gave a solid, which, upon crystallization from Skellysolve B, afforded 173 g. (88%) of 2,6-dichlorophenol, m.p. $64-65^{\circ}$; lit. m.p. $64.5-65.5^{\circ}$ (66).

4. Preparation of 2,6-Dibromophenol

A. 3,5-Dibromo-4-hydroxybenzoic Acid

This compound was prepared by the method of Grovenstein and Henderson (67), as follows. To a stirred suspension of 4-hydroxybenzoic acid (138 g., 1 mole, obtained from Eastman Organic Chemicals, Rochester, N.Y., U.S.A.) in glacial acetic acid (700 ml.) was added 640 g. (4 moles) of bromine. The resulting mixture was heated for 5 hours on a steam bath and then thoroughly cooled. The solid was collected by filtration, washed thoroughly with water and air-dried. Recrystallization from glacial acetic acid afforded 249 g. (84%) of 3,5-dibromo-4-hydroxybenzoic acid, m.p. $273-275^{\circ}$; lit. m.p. $275-276^{\circ}$ (67).

B. 2,6-Dibromophenol

Decarboxylation of 3,5-dibromo-4-hydroxybenzoic acid (148 g., 0.5 mole) according to the procedure described above for the corresponding dichloro compound (see the preparation of 2,6-dichlorophenol), afforded 112 g. (89%) of 2,6-dibromophenol, m.p. 55-56° (from hexane); lit. m.p. 56-57° (68).

5. Preparation of Ring-Halogenated Allyl Phenyl Ethers

Allyl 2,6-Dichlorophenyl Ether

To a solution of 2,6-dichlorophenol (81.5 g., 0.5 mole) in 200 ml. of water containing 30 g. of sodium hydroxide was added acetone (300 ml.) and allyl bromide (85 g., 0.7 mole). The resulting solution was refluxed, with stirring, for 3 hours, poured into 700 ml. of ice water, and then extracted thrice with ether. The combined ether extracts were washed several times with water and dried over anhydrous magnesium sulphate. Removal of the ether afforded an oil which, upon distillation under reduced pressure through a short Vigreux column, gave 91 g. (90%) of allyl 2,6-dichlorophenyl ether, b.p. 69-70° at 1 mm.; lit. b.p. 89-90° at 2 mm. (46).

Allyl 2,6-Dibromophenyl Ether

This compound was prepared by the above method. From 50 g. (0.2 mole) of 2,6-dibromophenol there was obtained 52 g. (90%) of allyl 2,6-dibromophenyl ether, b.p. 73° at 0.4 mm.; lit. b.p. 112-113° at 2 mm. (45).

Allyl 2-Chlorophenyl Ether

Purified grade o-chlorophenol, obtained from Fisher Scientific Company, Fair Lawn, N.J., U.S.A., was carefully distilled and then converted to allyl 2-chlorophenyl ether by application of the above method. From 64 g. (0.5 mole) of the phenol was obtained 75 g. (89%) of the ether. B.p. 100-102° at 11 mm.; lit. b.p. 108-110° at 15 mm. (46).

Allyl 2-Bromophenyl Ether

This compound was prepared by the method described above. From 75 g. (0.43 mole) of o-bromophenol (Eastman Organic Chemicals, Rochester, N.Y., U.S.A.) was obtained 78 g. (85%) of allyl 2-bromophenyl ether, b.p. 66-67° at 0.8 mm.; lit. b.p. 130-134° at 20 mm. (44).

Allyl 2,4-Dichlorophenyl Ether

This compound was prepared from 2,4-dichlorophenol (Matheson, Coleman and Bell, Norwood, Ohio, U.S.A.) by the above method. From 49 g. (0.3 mole) of the phenol was obtained 53 g. (86%) of allyl 2,4-dichlorophenyl ether, b.p. 73-73.5° at 0.55 mm.; lit. b.p. 144-145° at 20 mm. (69).

Allyl 2,4-Dibromophenyl Ether

By application of the above method, 76 g. (0.3 mole) of 2,4-dibromophenol (Eastman Organic Chemicals, Rochester, N.Y., U.S.A.) was converted to 84 g. (95%) of allyl 2,4-dibromophenyl ether, b.p. 90° at 0.4 mm.; lit. b.p. 127-134° at 0.5 mm. (44).

Allyl 2-Bromo-4-chlorophenyl Ether

This compound was prepared by the above method. From 62 g.

(0.3 mole) of 2-bromo-4-chlorophenol (Aldrich Chemical Co., Inc., Milwaukee 10, Wisconsin, U.S.A.) was obtained 65 g. (88%) of allyl 2-bromo-4-chlorophenyl ether, b.p. 82° at 0.5 mm., n_D^{25} 1.5757. Calc. for C_9H_8BrClO : C, 43.67; H, 3.26; Br, 32.29; Cl, 14.32. Found: C, 43.93; H, 3.26; Br, 32.61; Cl, 14.17.

Allyl 4-Bromo-2-chlorophenyl Ether

This ether was prepared by the method described above. From 21 g. (0.1 mole) of 4-bromo-2-chlorophenol (Aldrich Chemical Co., Inc., Milwaukee 10, Wisconsin, U.S.A.) was obtained 23 g. (92%) of allyl 4-bromo-2-chlorophenyl ether, b.p. $84-85^{\circ}$ at 0.7 mm. Calc. for C_9H_8BrClO : C, 43.67; H, 3.26; Br, 32.29; Cl, 14.32. Found: C, 43.68; H, 3.19; Br, 32.14; Cl, 14.51. n_D^{25} 1.5752.

6. Preparation of Ring-Halogenated 2-(and 4-)Allylphenols

2-Allyl-6-chlorophenol

A solution of allyl 2-chlorophenyl ether (34 g., 0.2 mole) in diphenyl ether (80 ml.) was heated with stirring, under an atmosphere of purified nitrogen, to $205-210^{\circ}$ and kept at this temperature for 3 hours. When the solution had cooled, it was diluted with 400 ml. of commercial pentane and extracted thrice with Claisen's alkali (52). The combined alkaline extracts were washed several times with pentane, thoroughly cooled in an ice-water bath, acidified with concentrated hydrochloric acid, and then thrice extracted with pentane. The combined extracts were washed with saturated salt solution and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was distilled under vacuum through a short Vigreux column, giving 31 g. (90%) of 2-allyl-6-chlorophenol, b.p. $71-72^{\circ}$ at 2 mm.;

lit. b.p. 215-220° at 750 mm. (46).

2-Allyl-6-bromophenol

This compound was prepared in an analogous manner to that described above. From 53 g. (0.25 mole) of allyl 2-bromophenyl ether was obtained 41 g. (77%) of 2-allyl-6-bromophenol, b.p. 59-60° at 0.7 mm.; lit. b.p. 87-88° at 2 mm. (44).

2-Allyl-4,6-dichlorophenol

This phenol was prepared from allyl 2,4-dichlorophenyl ether by the above method. From 45 g. (0.22 mole) of the ether was obtained 39 g. (87%) of 2-allyl-4,6-dichlorophenol, b.p. 77° at 0.9 mm.; lit. b.p. 264° at 759 mm. (70).

2-Allyl-4,6-dibromophenol

This compound was prepared as described above. From 58 g. (0.2 mole) of allyl 2,4-dibromophenyl ether was obtained 35 g. (60%) of 2-allyl-4,6-dibromophenol, b.p. 88° at 0.4 mm.; lit. b.p. 118-122.5° at 1 mm. (44).

2-Allyl-6-bromo-4-chlorophenol

This compound was prepared from allyl 2-bromo-4-chlorophenyl ether by the method described above. From 40 g. (0.16 mole) of the ether was obtained 30 g. (75%) of 2-allyl-6-bromo-4-chlorophenol, b.p. 80-81° at 0.6 mm.. n_D^{25} 1.5838.

Calc. for C₉H₈BrClO: C, 43.67; H, 3.26; Br, 32.29; Cl, 14.32.

Found: C, 43.82; H, 3.36; Br, 32.20; Cl, 14.07.

2-Allyl-4-bromo-6-chlorophenol

This compound was prepared as described above. From 21 g. (0.085 mole) of allyl 4-bromo-2-chlorophenyl ether was obtained

16 g. (76%) of 2-allyl-4-bromo-6-chlorophenol, b.p. 80° at 0.4 mm..

Calc. for C_9H_8BrClO : C, 43.67; H, 3.26; Br, 32.29; Cl, 14.32.

Found: C, 43.60; H, 3.31; Br, 32.08; Cl, 14.43.

n_D^{25} 1.5855.

4-Allyl-2,6-dichlorophenol

Rearrangement of allyl 2,6-dichlorophenyl ether (41 g., 0.2 mole) in 100 ml. of o-dichlorobenzene at 178° for 12 hours, followed by isolation and purification of the phenolic product as described above, gave 33 g. (80%) of 4-allyl-2,6-dichlorophenol, b.p. 75° at 0.5 mm.; m.p. $34-35^{\circ}$. Lit. b.p. $104-108^{\circ}$ at 3 mm.; lit. m.p. $33-35^{\circ}$ (46).

7. Preparation of Halogenated 2-Methylcoumarans

7-Chloro-2-methylcoumaran

The general procedure reported in the literature (14, 45) was employed to obtain this compound from 2-allyl-6-chlorophenol, as follows. To a solution of 2-allyl-6-chlorophenol (34 g., 0.2 mole) in glacial acetic acid (250 ml.) was added 50 g. of 48% hydrobromic acid. The resulting solution was refluxed, with stirring, for 3 hours, cooled, poured into 500 ml. of water, and extracted twice with ether. The combined ether extracts were washed several times with water, several times with aqueous sodium bicarbonate, twice with dilute aqueous sodium hydroxide, finally twice with water and then dried over anhydrous magnesium sulphate. Removal of the ether gave an oil which, upon distillation under reduced pressure through a short Vigreux column, afforded 19 g. (56%) of 7-chloro-2-methylcoumaran, b.p. 74° at 1.8 mm..

n_D^{25} 1.5496.

Calc. for C_9H_9ClO : C, 64.10; H, 5.38; Cl, 21.03.

Found: C, 64.17; H, 5.21; Cl, 21.24.

7-Bromo-2-methylcoumaran

This compound was prepared from 2-allyl-6-bromophenol by the procedure described above. From 21 g. (0.1 mole) of the phenol was obtained 12 g. (57%) of 7-bromo-2-methylcoumaran, b.p. 71° at 0.75 mm.. n_D^{25} 1.5735.

Calc. for C_9H_9BrO : C, 50.73; H, 4.26; Br, 37.51.

Found: C, 50.97; H, 4.21; Br, 37.26.

5,7-Dichloro-2-methylcoumaran

This compound was prepared from 2-allyl-4,6-dichlorophenol by a procedure analogous to that described above. From 18.3 g. (0.09 mole) of the phenol was obtained 8.8 g. (48%) of the 5,7-dichloro-2-methylcoumaran, b.p. 81° at 0.7 mm.. n_D^{25} 1.5640.

Calc. for $C_9H_8Cl_2O$: C, 53.23; H, 3.97; Cl, 34.92.

Found: C, 52.91; H, 4.08; Cl, 35.20.

5,7-Dibromo-2-methylcoumaran

This compound was prepared by the above procedure. From 20.5 g. (0.07 mole) of 2-allyl-4,6-dibromophenol was obtained 14 g. (68%) of 5,7-dibromo-2-methylcoumaran, b.p. 90° at 0.3 mm.; lit. b.p. $129-134^\circ$ at 1.0 mm. (45).

7-Bromo-5-chloro-2-methylcoumaran

This compound was prepared from 2-allyl-6-bromo-4-chlorophenol by the procedure described above. From 33 g. (0.13 mole) of the phenol was obtained 24 g. (73%) of 7-bromo-5-chloro-2-methyl-

coumaran, b.p. 95° at 0.9 mm.. n_D^{25} 1.5854.

Calc. for C_9H_8BrClO : C, 43.67; H, 3.26; Br, 32.29; Cl, 14.32.

Found: C, 43.71; H, 3.22; Br, 32.17; Cl, 14.53.

5-Bromo-7-chloro-2-methylcoumaran

This compound was prepared by an analogous procedure to that described above. From 37 g. (0.15 mole) of 2-allyl-4-bromo-6-chlorophenol was obtained 27 g. (73%) of 5-bromo-7-chloro-2-methylcoumaran, b.p. 99° at 0.8 mm.. n_D^{25} 1.5863.

Calc. for C_9H_8BrClO : C, 43.67; H, 3.26; Br, 32.29; Cl, 14.32.

Found: C, 43.47; H, 3.39; Br, 32.51; Cl, 14.42.

8. The Claisen Rearrangement of Allyl 2,6-Dihalophenyl Ethers under Various Conditions

Thermal Rearrangement of Pure Allyl 2,6-Dichlorophenyl Ether

A sample of allyl 2,6-dichlorophenyl ether (30 g., 0.15 mole) was heated with stirring, under an atmosphere of purified nitrogen to $193-200^{\circ}$ and kept at this temperature for 90 minutes. The cooled material was analyzed directly by v.p.c.. The results are shown in Expt. No. 1, Table II, page 72, and in Expt. No. 4, Table III, page 80.

Thermal Rearrangement of Allyl 2,6-Dichlorophenyl Ether in Various Solvents. General Procedure.

Dried and redistilled solvent (50 ml.) was stirred and heated, under an atmosphere of purified dry nitrogen, to the desired temperature for rearrangement, and then allyl 2,6-dichlorophenyl ether (10 g., 0.05 mole) was slowly added over a period of approximately

30 minutes. The resulting solution was heated for the time required for complete reaction of the original ether, cooled, and analyzed directly for products by v.p.c. by injecting aliquots of the total reaction mixture into the Kromo-Tog. The results are recorded in Table II, page 72, Table III, page 80, and in Table V, Section B, page 93.

Rearrangement of Allyl 2,6-Dichlorophenyl Ether in the Presence of Lithium Chloride

Anhydrous powdered lithium chloride (9.3 g., 0.2 mole) was stirred into dried, redistilled nitrobenzene (82 g., 0.67 mole) and the resulting mixture was heated, under an atmosphere of purified dry nitrogen, to 180-185°. Not all of the lithium chloride dissolved. After slow addition of allyl 2,6-dichlorophenyl ether (20 g., 0.1 mole), the mixture was heated at 180-185° for 3 hours. The cooled material was poured into a mixture of ether and water (1:1). After filtration, the ether layer was separated, washed twice with saturated salt solution, and dried over anhydrous sodium sulphate. Removal of the ether gave the mixture of reaction products and solvent, which was analyzed directly by v.p.c.. The results are shown in Expt. Nos. 3 and 5, Table II, page 72, and in Expt. No. 9, Table III, page 80.

Rearrangement of Allyl 2,6-Dichlorophenyl Ether in the Presence of Stannous Chloride

(a) Anhydrous powdered stannous chloride (9.5 g., 0.05 mole) was stirred into 50 ml. of dried, redistilled *o*-dichlorobenzene. After the mixture (a considerable portion of the stannous chloride

remained undissolved) had been heated to 150-155° under an atmosphere of purified, dry nitrogen, allyl 2,6-dichlorophenyl ether (10 g., 0.05 mole) was slowly added. The reactants were then heated at 150-155° for 24 hours, cooled, and poured into a mixture of water and ether (1:1). The resulting mixture was filtered and the layers were separated. The ether layer was washed several times with water and dried over anhydrous sodium sulphate. Removal of the ether afforded the mixture of reaction products and solvent, which was analyzed directly by v.p.c.. The results are recorded in Table V, Section A, page 93.

(b) Procedure (a) was repeated, employing 1.25 g. (0.006 mole) of allyl 2,6-dichlorophenyl ether and 2.5 g. (0.012 mole) of stannous chloride in 125 ml. of dried redistilled o-dichlorobenzene. Nearly all of the stannous chloride dissolved. After treatment of the cooled reaction mixture as described above, 50 ml. of o-dichlorobenzene was removed by careful fractional distillation under reduced pressure. The distillate was shown by v.p.c. to be pure solvent, containing no phenolic products. The residual solution was analyzed by v.p.c. and the results recorded in Table V, Section C, page 93.

The Zinc Chloride-Catalyzed Rearrangement of Allyl 2,6-Dichlorophenyl Ether. General Procedure.

Anhydrous powdered zinc chloride (41 g., 0.3 mole) was stirred into 150 ml. of dry ether. While the mixture was gently heated to permit evaporation of the ether, dried and redistilled nitrobenzene (123 g., 1 mole) was slowly added. After the result-

ing mixture (not all of the zinc chloride dissolved) had been heated to the desired temperature for the rearrangement, allyl 2,6-dichlorophenyl ether (30 g., 0.15 mole) was slowly added. The mixture was then stirred and heated under an atmosphere of purified, dry nitrogen for the specified time. The cooled material was poured into a mixture of water and ether (1:1). After filtration, the ether layer was separated, washed several times with saturated salt solution, and then dried over anhydrous sodium sulphate. Removal of the ether gave a mixture of reaction products and solvent, which was analyzed directly by v.p.c.. The results are summarized in Table I, page 67.

The Zinc Chloride-Catalyzed Rearrangement of Allyl 2,6-Dibromophenyl Ether. General Procedure.

Anhydrous powdered zinc chloride (14 g., 0.1 mole) was stirred into 50 ml. of dry ether. The mixture was gently heated to permit evaporation of the ether while dried, redistilled nitrobenzene (41 g., 0.33 mole) was slowly added. The resulting mixture was then heated to the desired rearrangement temperature. Not all of the zinc chloride dissolved. After slow addition of allyl 2,6-dibromophenyl ether (14.6 g., 0.05 mole), the reaction mixture was stirred and heated under an atmosphere of purified dry nitrogen for the specified time. The cooled material was treated as described above for the zinc chloride-allyl 2,6-dichlorophenyl ether reaction, and product analysis was carried out directly by v.p.c.. The results are shown in Table VII, page 105.

The Zinc Bromide-Catalyzed Rearrangement of Allyl 2,6-Dichloro-phenyl Ether. General Procedure.

Anhydrous powdered zinc bromide (22.5 g., 0.1 mole) was stirred into 50 ml. of dry ether. While the mixture was gently heated to permit evaporation of the ether, dried and redistilled nitrobenzene (41 g., 0.33 mole) was slowly added. After the resulting mixture (not all of the zinc bromide dissolved) had been heated to the desired temperature for rearrangement, allyl 2,6-dichlorophenyl ether (10 g., 0.05 mole) was added slowly. The reaction mixture was then stirred and heated, under an atmosphere of purified, dry nitrogen for the specified time. After treatment of the cooled material as described above, product analysis was carried out directly by v.p.c.. The results are recorded in Table VI, page 104.

9. Stability Tests on Products Under Reaction Conditions

A study was made to determine whether the products obtained in our reactions were stable under the reaction conditions. In all cases, by using an internal standard in v.p.c. analyses, the products from our reactions were shown, within experimental error, to be stable under the reaction conditions employed. However, in the case of the metal halide-catalyzed reactions, the 2-allylphenols were converted in part, or completely, to the corresponding stable 2-methylcoumarans and to no other product. In the case of the zinc halide-catalyzed reactions, the products were subjected to the most strenuous reaction conditions employed.

The procedure used throughout this study can be illustrated by the following example, which concerns the products obtained

from the thermal rearrangement of allyl 2,6-dichlorophenyl ether in nitrobenzene solution.

A mixture of 0.972 g. of 2-allyl-6-chlorophenol (A), 0.480 g. of 2-allyl-4,6-dichlorophenol (B) and 1.05 g. of 4-allyl-2,6-dichlorophenol (C) was heated in 25 ml. of nitrobenzene at 180-185° for 4 hours. To the cooled solution was added 0.988 g. of n-tetradecane (S) as internal standard, and the resulting solution was then analyzed by v.p.c.. From the v.p.c. chromatogram were obtained the ratios of the peak area of the internal standard to that of each of the products, as follows.

$$\frac{\text{Peak area of S}}{\text{Peak area of A}} = 1.23$$

$$\frac{\text{Peak area of S}}{\text{Peak area of B}} = 3.02$$

$$\frac{\text{Peak area of S}}{\text{Peak area of C}} = 1.45$$

An authentic mixture of nearly the same composition as the product mixture above was then prepared, as indicated below.

Wt. of 2-allyl-6-chlorophenol = 0.194 g. (A)

Wt. of 2-allyl-4,6-dichlorophenol = 0.092 g. (B)

Wt. of 4-allyl-2,6-dichlorophenol = 0.194 g. (C)

Wt. of n-tetradecane = 0.188 g. (S)

Analysis of this mixture by v.p.c. gave the following peak area ratios.

$$\frac{\text{Peak area of S}}{\text{Peak area of A}} = 1.16$$

$$\frac{\text{Peak area of S}}{\text{Peak area of B}} = 3.15$$

$$\frac{\text{Peak area of S}}{\text{Peak area of C}} = 1.45$$

The corresponding weight ratios in the authentic mixture are as follows.

$$\frac{\text{Wt. of S}}{\text{Wt. of A}} = 0.97$$

$$\frac{\text{Wt. of S}}{\text{Wt. of B}} = 2.04$$

$$\frac{\text{Wt. of S}}{\text{Wt. of C}} = 0.97$$

The absolute weights of the products in the original reaction mixture were calculated as follows.

$$\text{Wt. ratio of S/A in reaction mixture} = \frac{0.97 \times 1.23}{1.16} = 1.03$$

$$\text{Wt. of 2-allyl-6-chlorophenol (A)} = \frac{0.988}{1.03} = 0.96 \text{ g.}$$

$$\text{Wt. ratio of S/B in reaction mixture} = \frac{2.04 \times 3.02}{3.15} = 1.96$$

$$\text{Wt. of 2-allyl-4,6-dichlorophenol (B)} = \frac{0.988}{1.96} = 0.50 \text{ g.}$$

$$\text{Wt. ratio of S/C in reaction mixture} = \frac{0.97 \times 1.45}{1.45} = 0.97$$

$$\text{Wt. of 4-allyl-2,6-dichlorophenol (C)} = \frac{0.988}{0.97} = 1.02 \text{ g.}$$

Within experimental error, these calculated weights agree with those originally put in the reaction mixture.

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